NOV 19 1935

VOLUME LVII NUMBER 5

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BULLETIN of the JOHNS HOPKINS HOSPITAL

THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL
SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY

November, 1935

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PUBLISHED MONTHLY

THE JOHNS HOPKINS PRESS, Baltimore, Maryland

Made in United States of America

BULLETIN
OF
THE JOHNS HOPKINS HOSPITAL

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This periodical is issued monthly. Two volumes a year are issued, each consisting of approximately 400 pages, and beginning in January and July, respectively.

Subscription price. In the United States and its possessions $6.00 per year. In Canada $6.25 per year; in foreign countries $6.50 per year. Prices for back volumes and back single numbers on application. Single numbers of the current volume, when available, $.75. Prices are net, postpaid.

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THE JOHNS HOPKINS PRESS
BALTIMORE, MARYLAND, U. S. A.

Entered as second-class matter at the Baltimore, Md., Postoffice. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 3, 1918

EXPERIMENTAL STUDIES ON THE PATHOGENESIS OF EPITUBERCULOSIS

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From The Department of Pathology, Johns Hopkins University

Submitted for publication July 26, 1935

Since the publication in 1920 of Eliasberg and Neuland's (1) original cases of resolving pulmonary shadow occurring in children with a positive tuberculin reaction, a condition to which they applied the term "epituberculosis," many similar cases have been described, which, because of custom, are still designated as epituberculosis, although this term is a rather unfortunate and confusing one.

Clinically, the diagnosis of epituberculosis is applied to those tuberculin-positive children who develop a characteristic pulmonary x-ray shadow, which may arise suddenly or slowly, and which then gradually disappears. The clearing of the shadow requires from several months to a year or longer. The x-ray shadow is usually rather homogeneous in density, and is ordinarily wedge-shaped, with the base of the wedge on the pleura and its apex at the hilum. It may be located in any lobe, and sometimes involves an entire lobe. Its border is often sharply outlined by the interlobar fissure. During the gradual process of clearing, the area becomes progressively smaller, clearing proceeding from the margins rather than in spotty fashion. When it does not clear completely, a residuum of strands converging at the hilum may remain for years, and sometimes small foci of calcification remain after the original shadow has disappeared. McPhedran (2) has reproduced very good x-rays, pictures and diagrams of different stages of the process in his papers on the general subject of tuberculosis in childhood.

One is struck, in these cases, by the mildness of accompanying symptoms in comparison with those in cases of well defined progressive tuberculous pneumonia. The temperature is either normal or only slightly elevated. The children may feel very well subjectively and play about in a normal manner. Occasionally, however, other

manifestations of tuberculosis, such as tuberculids, phlyctenular conjunctivitis or bone and joint lesions may accompany the resolving pulmonary shadow.

In the tuberculosis clinic of the Harriet Lane Home for Invalid Children in the Johns Hopkins Hospital, benign pulmonary shadows of this nature have frequently been discovered accidentally during routine examination in children apparently in excellent health. An x-ray series (figs. 16, 17, 18) from a typical Harriet Lane case is reproduced through the courtesy of Dr. E. A. Park as a basis for comparison with the experimental work to follow. The patient was a boy, followed because of contact with a tuberculous father. Because of a positive tuberculin reaction at 3 months, in spite of a normal physical examination and no symptoms, a chest plate was taken and revealed a mediastinal shadow, diagnosed as tuberculous mediastinal nodes, and a slight continuation of this shadow into the right lung. At 5 months he continued to look and act like a normal infant; his temperature ran a normal course; and his chest findings were not abnormal. Yet his x-ray revealed an extensive homogeneous shadow in the right upper lobe. Five weeks later, this had undergone no change; then resolution began, the wedge becoming gradually smaller by clearing at all of its borders. Not until almost a year later had it cleared entirely, and then a residual mediastinal shadow remained, with the linear marking of the transverse interlobar fissure.

It is exceedingly difficult and often impossible to differentiate the shadow of this benign condition, epituberculosis, from the shadow produced by a tuberculous pneumonia that will spread progressively with a fatal termination. Both occur in tuberculin-positive children, and both may be of the same extent and configuration and develop in the same manner, while the onset of the latter may be as mild, clinically, at times, as that of epituberculosis. It would obviously be very important to be able to decide clinically whether a discovered shadow of this character will turn out to be benign and will clear completely or whether it will proceed to a progressively spreading fatal tuberculosis. To this end it is highly desirable that the precise nature of the benign condition be understood, for at present there is great confusion regarding both its etiology and its pathogenesis.

Before stating the working theory used in the present experiments,

which was formulated by Dr. Arnold R. Rich, and which I have tried to elaborate by reproducing the condition of epituberculosis experimentally, previous views concerning the nature of the condition, as well as all of the pertinent autopsy material that has been published, may be briefly reviewed.

Autopsy material is obviously needed to ascertain with certainty exactly what is happening in the lung in epituberculosis. However, in spite of the fact that this benign type of pulmonary consolidation in childhood tuberculosis occurs frequently and has often been described and discussed from a clinical standpoint, the precise nature of the lesion is not yet known for the reason that, since the condition itself is not fatal, the opportunity for an autopsy depends upon the accidental death of the patient from some other cause, and this has greatly limited the opportunity for a thorough study of the pathogenesis of the condition. Autopsy studies on authentic cases have, therefore, been rare, and unfortunately none of the material published to date is entirely satisfactory. Either the clinical picture was not definitely that of epituberculosis; or, if the case was interpreted as epituberculosis clinically, there was found at autopsy a progressive and fatal tuberculosis; or else the lesion had so far resolved that its mode of origin and the state of its earlier appearance could not be reconstructed; and, finally, the descriptions of the pathological material are often inadequate from the standpoint of recording crucial details.

The case of Eliasberg and Neuland (1), which was the first to be reported, was that of a 19 months old child who died of an intercurrent pneumonia and empyema after showing clinically at 11 months a positive tuberculin reaction, and an infiltration of the right upper lobe for which he received pneumothorax treatment. The writers felt that the pathological picture was altered by the pneumothorax as well as by the intercurrent infection causing death. They stated that at autopsy they found no tuberculosis at the site of the x-ray shadow, but only a pneumonic exudate of "small round cells." No note was made concerning the condition of the hilum nodes. On the basis of this case they considered epituberculosis to be a non-specific pneumonia in a young patient with tuberculosis, the tuberculosis having been demonstrated as present by means of the tuberculin reaction. Yet, as pointed out by Reichle (3), there are pictures borrowed from this case in a textbook published by Pagel and Henke (4), which strikingly suggest that the consolidation of "small round cells" was tuberculous, for the exudate pictured resembles a tuberculous pneumonia consisting of epithelioid cells, without, however, any caseation.

Grävinghoff's case (5) is that of a girl 35 months old, who died of an intercurrent infection more than a year after the resolution of the shadow of the epituberculosis. Clinically, signs of consolidation over the right upper lobe were discovered when the child was examined for phlyctenular conjunctivitis. The tuberculin reaction was positive. Subsequently the lung findings of bronchial breathing and dry râles were unchanged, although the patient developed chickenpox, measles and diphtheria in the next 7 months. In the 8 to 10 months following the discovery of the consolidation, the x-ray shadow became less dense. In spite of pertussis in the next interval, by the fifteenth month it had resolved except for a few streaks. At the eighteenth month the clinical signs were gone and the x-ray was entirely clear. A year later the child was again seen and died following an acute illness of only 12 hours' duration. At autopsy, there was a lobar pneumonia of both lower lobes and emphysema of the upper lobes. Old pleural adhesions were found on both sides. Large lymph nodes were seen along the trachea and a small calcified node was noted at the right hilum. Microscopically, in the former area of the epituberculosis, the lungs showed an increase of connective tissue in the septa of lobules and alveoli, and calcification in the right hilum node. This fails to show the nature of the process of the active epituberculosis, but proves that resolution occurred with only slight residual scarring, leaving no indication in the parenchyma of the specific nature of the preceding process.

The 3 cases published by Engel (6) as epituberculosis are so incomplete that no definite conclusions can be reached. One case occurred in an 18 months old boy who, while being treated for congenital syphilis, was tested with tuberculin and gave a positive reaction. Later, there was an acute onset of fever and clinical signs in his right upper lobe were diagnosed as pneumonia. However, no typical resolution occurred and the x-ray showed a persisting hilum shadow called hilum tuberculosis because of the positive tuberculin reaction. Recuperation was slow; the child showed the picture of a "slowly developing tuberculosis," details of which are not given. He developed multiple infections, pertussis, diphtheria, "etc." The course of his pulmonary condition and mode of death are not stated. At autopsy, Engel recognized nowhere any pulmonary tuberculosis, only "old and fresh" pneumonic consolidations. The bronchial nodes were large and red. After much search a caseous and calcified node was found. In summarizing this case, he stated that the chief interest lay in the acute high-fevered onset of the infiltration. He considered the tuberculosis trifling; its action on the body barely discernible through the tuberculin reaction. He concluded that it must be called a chronic progressive pneumonia. In the absence of microscopic notes, the etiology of this case is still unexplained.

Engel's second case is that of a 2-year-old boy, whose illness at first resembled epituberculosis. He had evidently been ill for some time before his first examination, with signs pointing to a pneumonia of the left upper lobe. This consolidation spread upward, cleared below, and then remained stationary. The tuberculin test was positive. His fever rose, and when his condition became worse, an x-ray

showed a typical pulmonary miliary tuberculosis. The progressive pulmonary tuberculosis found at autopsy failed to clarify the subject of epituberculosis.

Engel's third case, also a 2-year-old boy, at first seemed in good health except for tuberculids and a positive tuberculin reaction. However, x-ray examination showed that his entire right upper lobe was deeply infiltrated; percussion was dull and breathing bronchial. There were only a few râles. His condition remained stationary for a month, after which vertebral tuberculosis developed. Death occurred soon from tuberculous meningitis. No further mention of the clinical status of the lung condition was made, nor was the exact time interval before death given. At autopsy, the left lung was normal as were its hilum nodes. The right lung was tightly adherent to the chest wall, firm and greyish red in color. Macroscopically, no tuberculous areas were seen. There were caseous hilum nodes on the right containing some calcification. Again, in the absence of microscopical notes and of any mention of whether or not the process had cleared clinically, the final report that the lung was "free from tuberculosis" does not clarify the situation.

Epstein's case (7) was in a boy, who at 4 months of age developed a diffuse bronchitis and was found to have a positive tuberculin reaction. Two weeks later, the percussion note seemed dull over the left upper lobe, breath sounds were bronchial and there were a few râles. X-ray showed a homogeneous shadow of the left upper lobe, reaching from hilum to periphery. Symptomatically, the child seemed well and was afebrile. There was occasional bitonal cough. No tubercle bacilli were found in the sputum. The chest findings remained unchanged until, at 11 months, death occurred following a miliary tuberculosis and tuberculous meningitis. At autopsy, the area of the homogeneous x-ray shadow was thought to be a combination of atelectasis, enlarged caseous hilum nodes and a firm tissue at the periphery of the lobe composed of a dense mass of tubercles about a healing caseous focus, which was regarded as probably representing a primary focus. The mechanism of the production of the atelectasis was not discussed but, from the illustration, it seems to have resulted from bronchial occlusion by the enlarged tuberculous hilum nodes.

This last case is strikingly similar to one autopsied in this department by Dr. Rich (Autopsy No. 10477). It was a case of a 20-months-old colored girl, who clinically showed loss of weight and appetite, cough, and temperature ranging from 99.2°F. to as high as 102°, but which returned to normal after a period of 3 weeks. Her tuberculin reaction was positive. An x-ray showed consolidation of the right upper lobe. Physical examination revealed only impaired percussion. After following her in the dispensary for 3 weeks a diagnosis of epituberculosis as made, although no further x-rays were taken. Following an interval of 3 months during which the child

had been entirely well symptomatically, she suddenly became ill with signs of acute intestinal obstruction and generalized peritonitis, and died 5 days later. The autopsy showed that the peritonitis was due to the perforation of a tuberculous intestinal ulcer. There was generalized miliary tuberculosis. But most interesting were the lung findings. There was a small caseous encapsulated tuberculous nodule in the right lung about 6 mm. in diameter and a similar lesion in the lower lobe of the left lung. Both of these nodules had the characteristics of primary lesions. There were huge caseous peribronchial, bronchial, and peritracheal lymph nodes. In the periphery of the upper lobe of the left lung 1.5 cm. below the apex was a dense, sharply outlined, encapsulated, wedge-shaped, caseous mass, 2 cm. by 1.5 cm. in size, surrounded by a grey translucent zone of connective tissue. This had the appearance of an area of caseous pneumonia due to the rupture of a caseous lymph node into a bronchus, except that it was rather smaller and better encapsulated than such areas usually are. At the first bifuracation of the bronchus going to the upper lobe, a caseous lymph node was found to stretch the overlying bronchial wall until it was very thin. At this point, there was a distinct ulceration in the mucosa, the base of which, however, was healed ever with epithelium. Distal to this, was a small caseous mass, projecting into the bronchus but not yet ruptured. The conclusion was reached that the healed bronchial ulcer had been the site of discharge of material causing the wedge-shaped consolidation. The large caseous node beneath the ulcer had so greatly compressed the upper branch of the bronchus that it had caused atelectasis in the portion of the lung supplied by it. Dr. Rich considered the case to bear definitely upon the subject of epituberculosis. The wedge produced by the caseous discharge was encapsulated and not spreading. Had this area healed with shrinkage and had the patient lived, the case would have been considered as one of epituberculosis. Had it been actively progressing, it woud have been one of frank tuberculosis. It semed probable that it represented a stage intermediate beween frank progressive tuberculosis and epituberculosis.

The cases reported by Schlack (8), Leitmann (9) and Sonnenfeld (10) will not be discussed because, owing to the fact that all of them at autopsy showed progres-

sive tuberculosis, they throw no definite light on the subject of epituberculosis, even though at their onset the cases may have suggested this process.

The most interesting pathological report is a biopsy study made by Rubenstein (11) on a case in which the x-rays showed in series a typical epituberculous shadow with complete resolution. The case was that of a girl who at the age of 6 had her fourteenth attack of "grippe." Following this she developed a cough. Her x-ray reading was "distinct enlargement of bronchial nodes; massive mediastinal shadow, right root; pulmonary tissue normal." The diagnosis of mediastinal tuberculosis was made. Two months later, the child became worse; her cough was severe but unproductive of sputum. No tubercle bacilli were found. The temperature rose as high as 104°F. An x-ray showed a heavy shadow in the right middle lobe extending from hilum to periphery, in addition to large hilum nodes. A diagnosis of empyema was made. Following an unsuccessful attempt to drain off fluid, a rib was resected. The thickened pleura was found to cover a lung, so firm that it was thought to be a tumor, and a bit of tissue was, therefore, removed. This biopsy, which was made when the lung shadow was at its height, showed a pulmonary consolidation typical of tuberculosis, with giant cells, epithelioid cells, lymphocytes, fibroblasts and small areas of caseation. No tubercle bacillus stain was made, but the lesion had all the characteristics of tuberculosis. As stated above, the subsequent clearing of the area was followed in serial x-rays.

The case of Morlock and Pinchin (12) was of a 14-year-old boy, who had noticed slight loss of weight and appetite for 3 months. He had been coughing for 3 nights. Physical examination revealed marked impairment of the percussion note at the right apex with bronchial breathing in this area. There were no râles. The tuberculin test proved to be positive, but no tubercle bacilli could be found in the sputum or faeces. His x-ray showed an obvious hilum node and a homogeneous shadow with a sharp lower margin, typical of epituberculosis. A bronchoscopic examination was made and revealed a mass compressing the bronchus. A biopsy of this showed it to be tuberculous granulation tissue combined with lymphoid tissue, obviously a tuberculous lymph node. Four days later, another x-ray showed that the apex was clear, and this was interpreted as the reëxpansion of the lung in this area. Two weeks later, the shadow recurred and cleared again in 3 weeks. On the basis of the biopsy, Morlock and Pinchin explained the x-ray shadow as pulmonary atelectasis due to the pressure of a tuberculous node on the bronchus. Indeed, the rapid disappearance of the shadow indicates that it was caused by atelectasis, and although the x-ray picture reproduced is difficult to differentiate from epituberculosis, the rapidity of the clearing was much greater than that seen in epituberculosis. The relation of the shadows of atelectasis to the problem of epituberculosis will be discussed later.

Goldberg and Gasul (13) report the case of a 6-year-old boy with a positive tuberculin reaction, whose x-ray series showed a consolidation of the right upper lobe with resolution in 9 months. Following a second tuberculin test, using the Dermatubin test, 3¼ months later, the shadow and clinical signs of bronchial breathing over the entire right lung reappeared, accompanied, also, by a general-

ized reaction. Serial x-rays again showed a gradual resorption of the infiltrate. When seen again almost 4 months later, he had developed tuberculous peritonitis, and there was again impaired resonance and also diminished breath sounds over the right lung. His condition became worse and he died 16 months after he was first seen. At autopsy, the lungs showed caseous right hilum nodes with erosion of a main branch of the right upper bronchus. There was caseous pneumonia of the right upper lobe. Goldberg and Gasul concluded that the condition of the lungs was tuberculous from the outset, and that although the final condition in this case was that of a spreading tuberculosis, epituberculosis is always of a tuberculous nature. They did not add any discussion of the mechanism by which it is produced.

Spence (14) reported 3 clinical histories of tuberculin-positive children, the first two showing the typical course and x-rays of retrogressive pulmonary shadows with clearing. No pathological study was made of these cases. In the third case, lung punctures were made in the attempt to determine the etiology of the process. At 7 months of age this child had dullness over the left upper lobe, diminished breath sounds, a normal temperature and a strongly positive tuberculin reaction. The x-ray showed a dense wedge-shaped shadow in the middle and upper part of the left lung. Two lung punctures were made, 6 weeks apart, both yielding a small amount of caseous material containing stainable tubercle bacilli. The material from the first puncture was inoculated into a guinea-pig and produced a typical tuberculosis. Unfortunately, subsequently to the lung punctures, there had been only slight change in the x-ray, so that the final clinical course of the case is not known.

Görter and Lignac (15) report the case of a girl, 3 years of age, whose x-ray revealed a dense shadow in the right lung. She had been clinically ill for some time before with repeated attacks of bronchitis. A lung puncture was done to see if the shadow was due to a pleural exudate, and a drop of pus was obtained which contained pneumococci, type II, and tubercle bacilli as proved by guinea-pig inoculation. Eighteen months later, the shadow had greatly decreased in size, although it still extended to the periphery of the lung. The child died of tuberculous meningitis at about this time. An autopsy showed enlarged mediastinal glands; a left hilum node contained a small caseous focus. There were fibrous pleural adhesions over the right upper lobe. At the root of the right middle lobe was a caseous, partly calcified nodule, about the size of a marble. Beyond this, the pulmonary tissue showed an extensive proliferation of connective tissue, in which were epithelioid cell tubercles with scattered giant cells.

On the other hand, Loots (16) stated that in 2 typical cases which he followed with clearing x-ray shadows, lung punctures were performed while the x-ray shadows were slowly resolving, but that he was unable to obtain any tubercle bacilli. He did not mention the character of the material that was yielded by the punctures.

Finally, a case was reported by Rothman (17) of a child whose age is not given. Following a pulmonary consolidation of 9 months' duration, miliary tuberculosis developed. After this time the consolidation began to clear and had almost re-

solved before death occurred. Autopsy confirmed the diagnosis of miliary tuberculosis. Rothman stated that in the area of the x-ray shadow there were "small areas of consolidation" that could not be differentiated from those of an ordinary tuberculous pneumonia. He did not describe the condition of the hilum nodes. He felt that the early course, details of which he did not report, was characteristic of epituberculosis, and that later tubercle bacilli were disseminated, causing a generalized tuberculosis.

A wealth of additional clinical histories have been published with as many attempts to reconstruct the pathological nature of the process; but no further authentic pathological reports have been made. Reichle (3) has recently summarized the various theories which have been suggested regarding the nature of the condition as follows:

(1) The shadow may be caused by atelectasis from the pressure of enlarged tuberculous mediastinal nodes. (2) It may be caused by a chronic non-tuberculous pneumonia in a lung made more susceptible by the presence of a tuberculous infection. (3) It may be non-inflammatory, either caused by oedema or by connective tissue. (4) It may be caused by a retrogressive tuberculous pneumonia. Reichle thinks that the last explanation is probably the most plausible one.

From all of the above reports, in spite of lack of uniformity, the evidence indicates that, although atelectasis from obstruction of a bronchus by enlarged tuberculous lymph nodes is a definitely possible explanation of some widespread pulmonary shadows, it can hardly explain the typical clinical course of epituberculosis with its *slowly* resolving shadow. The clearing of a shadow caused by atelectasis would occur more rapidly once air was able to find its way past the obstruction, and the clearing would proceed throughout the entire area rather than begin at the margins and progress slowly over a period of months toward the hilum, as is so commonly the case in epituberculosis. Since, in every case in which the area has been examined pathologically, even in those in which atelectasis has been present, there have been found lesions typical of tuberculosis in the affected part, one cannot escape the conclusion that the massive pulmonary shadow of epituberculosis most probably is due to an area of tuberculous pneumonia, which resolves completely, or leaves foci of calcification or scars at its former site. But what is the mechanism of the origin of this peculiar form of tuberculosis, and what is responsible for its benign course?

It has been suggested by Dr. Rich that the mechanism of the formation of the shadow of epituberculosis is probably identical with that

responsible for the familiar progressive wedge-shaped shadow of caseous pneumonia which it simulates so closely, but that the actual material which produces the consolidation differs from that which causes the progressive wedge-shaped lesion, in that in the case of epituberculosis fewer viable bacilli are present in the material which incites the consolidation in the lung. The reasons for this view may be briefly summarized as follows:

In the case of the spreading caseous pneumonia, autopsy studies have amply shown that the wedge-shaped area of consolidation is produced by the rupture of a caseous lymph node, rich in tubercle bacilli, into a bronchus. The characteristic wedge-shaped x-ray shadow produced depends entirely on the bronchogenic distribution of the tubercle bacilli, for material distributed through a portion of the lung by way of a bronchus always occupies an area of that character. The progressive spread of an isolated focus situated in the substance of the lung leads to the formation of an area with a more circular or irregular outline In the case of the discharge of a caseous node, containing many viable bacilli, into a bronchus, a wedge-shaped area of consolidation is produced, but because of the many bacilli, the process is a progressive one, causing tuberculous pneumonia with caseation and leading to death.

The shape and appearance of the shadow of epituberculosis is identical with that produced by the discharge of a caseous node into a bronchus. So much so, indeed, that it is not possible to foretell from an examination of a single x-ray plate whether the process will spread progressively and lead to death or whether it will resolve completely. Since we know that shadows of this shape are commonly produced by a bronchogenic distribution of bacilli, it is reasonable to suppose that a bronchial distribution is also responsible for the shape of the shadow in epituberculosis. In the case of epituberculosis, however, the process resolves completely, or at most leaves only small scars or little foci of calcification. It must be clear, therefore, that the lesion cannot be due to the discharge of large numbers of viable bacilli from a caseous node into a bronchus, for such an accident would lead to progressive tuberculosis. However, since it has been shown by Rich and McCordock (18) and by others that the injection of tuberculin into a bronchus in an hypersensitive animal

causes a pneumonic consolidation which can resolve completely, and since it is well known that stainable bacilli often become very difficult to find in caseous lymph nodes, whereas in the early stages of the necrotizing process they are very abundant there, it seems not improbable that the walls of bronchi may become eroded during the active enlargement and caseation of adjacent nodes and that the final perforation of the mucosa may occur either when the node is heavily laden with viable bacilli, or at a time when most of the bacilli have died. The caseous material of the node, however, still contains tuberculoprotein in the bodies of the dead bacilli, as well as that liberated from disintegrated bacilli, and such caseous material discharged into the bronchus would incite a reaction comparable to that caused in the allergic lung by tuberculin. Having reached its height, it could resolve completely, or if the process were more severe, scarring or calcification of necrotic foci could result. To reiterate, this view suggests that epituberculosis may be the result of the discharge into a bronchus, in an allergic individual, of caseous material impregnated with tuberculoprotein, dead bacilli, and their fragments, but containing too few living bacilli to produce progressive tuberculosis in the face of the degree of acquired immunity established by the primary injection. Instead, there occurs a tuberculous pneumonia, incited chiefly by dead bacilli and tuberculoprotein-impregnated material discharged into the lung from the ruptured node, and this pneumonia will undergo gradual retrogression because of the absence of a sufficient number of living bacilli to produce a progressive lesion in the particular body affected. The fact that one encounters every gradation between progressive tuberculosis resulting from bronchial rupture and resolving epituberculosis, and further, the fact that calcified foci can sometimes be seen as residues of resolved epituberculosis, as well as the available pathological studies mentioned above, unsatisfactory as they may be, all lend weight to the view that the process is really a tuberculous consolidation, and not some mysterious non-tuberculous process occurring only in tuberculous individuals, as has so often been suggested.

That the healing and resolution of an area of tuberculosis produced in the lung by the discharge of a caseous node into a bronchus can occur is evident from four cases studied in this department by Dr.

Rich. Three of these cases were in adults (Autopsies nos. 10365, 11655, 11880). In each of these cases there was found a destruction of the bronchial wall, the site of the destruction being represented by hyalinized and caseous material continuous with an immediately adjacent hyalinized and caseous lymph node. The entire wall in each case was destroyed, the inner surface showing plainly a depressed scar of a former ulceration which was covered over by a layer of regenerated epithelium. In each case, in the area of the lung to which the bronchus led, there were found diffuse scars, and in two of the cases there were a number of encapsulated caseous and hyalinized nodules embedded in the scars. The fourth case (Autopsy no. 11249) was in a six-year-old child who died of tuberculous meningitis resulting from the extension of a caseous cerebellar tubercle. In this case there was still at the time of autopsy an ulceration in a bronchus the base of which was formed of a mortar-like material which was continuous with a caseous lymph node that had eroded the bronchial wall. There were no stainable bacilli in the mortar-like, caseous node. In the portion of the lung to which the eroded bronchus led there were diffuse scars, but no definite tuberculous tissue. This was learly a case in which a caseous node had eroded a bronchus and had discharged material into the lung, leading to an inflammatory reaction with some death of tissue, resolution of the exudate and scarring. There is every reason to believe that these four cases represent the residue of healed epituberculosis and this particularly since, as we shall see, similar residues were found in the lungs of the animals in the present experiments in which the essential features of epituberculosis have been reproduced.

On the basis of these considerations, an attempt was made to determine whether the clinical picture of epituberculosis could actually be produced by the introduction of dead bacilli into a bronchus of an animal; and if so, whether the hypersensitive state plays a rôle in the process, and what the nature of the pathological process may be during the development and resolution of the area of consolidation. These experiments have made it clear that by this method, at least, the typical clinical and x-ray characteristics of epituberculosis can be produced.

EXPERIMENTAL STUDIES

Three series of experiments were performed. In all cases the rabbit was the animal used. The rabbits were made hypersensitive by injecting subcutaneously a saline emulsion of either virulent (H37) or attenuated (R1) human type tubercle bacilli. Both of these strains of these strains of tubercle bacilli, as well as the virulent bovine bacilli (B1) to be mentioned below, were obtained from Dr. Leroy Gardiner, Director of the Saranac Laboratory. The rabbits were regarded as satisfactorily hypersensitive when they reacted well to an intradermal dose of 10 mg. of Old Tuberculin.

Table I summarizes the results of the first series, started April 1, 1934. A hemogeneous but heavy suspension of bovine bacilli (B1) was made in normal salt solution, using the entire growth from a single agar slant to 20 cc. of saline solution. Of this suspension 3 cc. was injected gently with a no. 21 B.D. needle between the tracheal cartilages of two allergic rabbits. The animals were held on their right sides during this procedure and for several minutes afterwards, in order to attempt to localize the material injected in a right bronchus. The bacilli in the remainder of the suspension were killed by heating for one hour at 100°C. After agitation of the suspension, 3 cc. were injected intratracheally in the manner just described into 15 allergic rabbits. Four control rabbits, all allergic, were injected intratracheally with sterile salt solution.

The rabbits were x-rayed at the following intervals after their injection; at 24 and 48 hours, 1, 2, 3, 5, 7, 8 and 10 weeks, and 5 months. The 4 saline control rabbits at no time showed any abnormal x-ray shadow. Two of them were killed at 8 and 9 weeks, respectively, and showed no pulmonary lesion either in the gross or microscopically.

The 2 rabbits which had been immunized and rendered hypersensitive by the previous subcutaneous injection of virulent human bacilli, and then inoculated intratracheally with living bovine bacilli showed a progressive x-ray shadow, beginning on the right and spreading to the left lung. One rabbit, no. 32, died in 5 months and showed at autopsy a widespread caseous pneumonia in which myriads of tubercle bacilli were stained. There were also tubercles in the viscera. The other rabbit, no. 31, lived much longer, but finally died in 11½ months with a chronic pulmonary tuberculosis with cavity formation. There was also generalized tuberculosis.

TABLE I

RABBIT NUMBER	SENSITIZED WITH	INTRA-TRACHEAL INJECTION 3 cc.	X-RAY SHADOW					TIME OF RABBIT'S DEATH	LESION AT AUTOPSY		
			Site	Character	Appeared	Maximum density	Disappeared		Gross	Microscopic	Tubercle bacilli
32	H_{37}	Living B_1	Bilateral	Spreading	24 hrs.	8 wks.	Persisted	5 mos. (D)*	Caseous pneumonia	Caseous pneumonia	+
31	H_{37}	Living B_1	Bilateral	Spreading	24 hrs.	8 wks.	Persisted	11½ mos. (D)	Caseous pneumonia	Organizing caseous-pneumonia	+
25	H_{37}	Saline	0	0	0	0	0	0			
26	H_{37}	Saline	0	0	0	0	0	Used in Series II	—	—	—
46	R_1	Saline	0	0	0	0	0	8 wks. (K)*	0	Normal	0
45	R_1	Saline	0	0	0	0	0	9 wks. (K)	0	Normal	0
40	R_1	Killed B_1	Rt. upper	Localized	48 hrs.	2–3 wks.	—	3 wks. (K)	Consolidation	Tuberculous pneumonia	+
39	R_1	Killed B_1	Rt. upper	Localized	1 wk.	2–3 wks.	Residual pleural line	8 wks. (D)	No autopsy		
42	R_1	Killed B_1	Rt. upper	Localized	48 hrs.	3–5 wks.	Trace remains 8 wks.	8 wks. (K)	Consolidation	Organizing tbc. pneumonia	+
44	H_{37}	Killed B_1	Rt. upper	Localized	1 wk.	3 wks.	10 wks.	14 wks. (D)	No autopsy		
34	R_1	Killed B_1	Rt. lower	Localized	48 hrs.	2–3 wks.	7 wks.	5½ mos.	Normal	Small scars and enlarged intrapulmonary lymphoid nodules	0
36	R_1	Killed B_1	Both lungs	Diffuse	48 hrs.	2 wks.	7 wks.	Used in Series II	—	—	—
33	H_{37}	Killed B_1	Rt. lung	Diffuse	24 hrs.	—	—	Used in Series II	—	—	—
50	H_{37}	Killed B_1	Rt. lung	Diffuse	24 hrs.	—	—	—	—	—	—
35	H_{37}	Killed B_1	0	—	—	—	—	—	—	—	—
30	H_{37}	Killed B_1	0	—	—	—	—	—	—	—	—
43	R_1	Killed B_1	0	—	—	—	—	—	—	—	—
48	H_{37}	Killed B_1	0	—	—	—	—	—	—	—	—
49	H_{37}	Killed B_1	0	—	—	—	—	Used in Series II	—	—	—
38	R_1	Killed B_1	0	—	—	—	—	—	—	—	—
41	R_1	Killed B_1	0	—	—	—	—	Used in Series II	—	—	—
62	Non-allergic	Killed B_1	0	—	—	—	—	Used in Series II	—	—	—

* D = died; K = killed.

Seven of the 15 allergic rabbits injected intratracheally with killed bovine bacilli showed no x-ray shadow. They were not autopsied. Two other rabbits developed indefinite shadows difficult to interpret, and these, also, were not killed. It was assumed that the injected bacilli were spread diffusely in these animals instead of being localized sufficiently to produce a homogeneous area of consolidation. Six rabbits, however, developed localized x-ray shadows, which in 5 cases were in every way similar to those seen clinically in children with epituberculosis. These shadows were in most cases localized in the right lung, although in one rabbit similar shadows were also seen in the left lung in addition to the right. The earliest appearance of the shadows was at 48 hours, but in some cases they first became visible in the x-ray taken at the end of a week. They spread and reached their maximum density slowly, taking an average of 3 weeks, and then resolved slowly, taking 7 weeks usually, but at the most 2½ months, to clear completely from an x-ray standpoint.

Three of these rabbits were killed and autopsied at different intervals after the injection. Rabbit no. 40, which was killed 3 weeks after the injection, developed at 48 hours some cloudiness of the right upper lobe, which at 1 week was definitely denser, and at 2 weeks was a sharply outlined consolidation of the lower two-thirds of the right upper lobe, reaching from the root to the periphery. At 3 weeks this showed no further change—the apex of the lung was still clear and the lower border of the consolidation coincided with the interlobar fissure. At this point the rabbit was killed. There was found in the region of the x-ray shadow an area of consolidation, measuring 2.5 cm. by 4.5 cm. (Fig. 3). Microscopically (Fig. 4) this was found to be a typical tuberculous pneumonia, with epithelioid and giant cells and considerable caseation of the exudate as well as of the alveolar walls. Many tubercle bacilli were stained in this lesion. There was no tuberculosis in the other viscera.

Rabbit no. 42 was killed at 8 weeks after the intratracheal injection. At 48 hours this animal showed a shadow between the 3rd and 5th ribs on the right side, reaching from the hilum two-thirds of the way to the periphery. At 2 weeks it extended from the apex down to the level of the 6th rib, but its height was reached between 3 and 5 weeks when it extended uniformly to the pleura. At 2 weeks there were also some spotty shadows in the left lung, which had cleared entirely at 5 weeks. At 7 and 8 weeks, the shadow in the right lung was resolving, its apex having cleared and its lower margin stopping in the 4th interspace. The wedge, however, still stretched to the pleura in the 3rd interspace. This rabbit was killed at the end of the 8th week and showed patchy areas of tuberculous pneumonia, smaller than the extensive area found in rabbit no. 40. These were localized in the posterior portion of the right upper lobe and showed peripheral organization and scarring about the pneumonic areas. Tubercle bacilli were stained in the areas of tuberculous pneumonia. Again there was no tuberculosis in the other viscera.

Rabbit no. 34 was killed 5½ months after the intratracheal injection with killed bacilli, and 3½ months after the x-ray shadow had cleared. At 48 hours, it showed

* D = died; K = killed.

some cloudiness of the right lower lung field. At 2 weeks the entire right lung contained a shadow reaching from its root to the periphery. At 3 weeks this was unchanged, but at 5 weeks it was resolving in a blotchy manner. It had resolved completely by 7 weeks. The last x-ray was taken at 5½ months and was entirely normal. The rabbit was then autopsied and showed in the gross no lesion, but microscopically there were strands of connective tissue and enlargement of the intrapulmonary lymphoid follicles in the right lung. No tubercle bacilli could be stained nor was there any lesion suggestive of tuberculosis.

The histories of the 3 rabbits that were not autopsied are as follows; Rabbit no. 39, at 1 week, showed a faint shadow between the 2nd and 5th right ribs. At 2 weeks there was a dense shadow extending almost from the apex to the level of the middle of the 5th interspace. This began to resolve at 5 weeks, and at 7 weeks the lung was clear except for a residual pleural line.

Rabbit no. 44 showed at 1 week a faint wedge between the level of the 4th and 5th right ribs. At 3 weeks, there was a dense shadow extending from the hilum to the periphery between the 3rd and 5th ribs. At 5 weeks, it was fading at all of its margins, and at 8 weeks, it was much fainter. The lung was clear at 10 weeks.

In rabbit no. 36, the shadow was not so well localized as in the other rabbits. It first showed at 48 hours as a clouding of the entire right lung field, and by 2 weeks the shadow was much more dense. At 3 weeks it was spotty in character. The spots were blurred at 5 weeks and the lung was entirely clear again at 7 weeks. In other words, although this rabbit developed a definite x-ray shadow following its injection, it was not a characteristic one.

In the second series of experiments, started in September, 1931, only 6 hypersensitive rabbits were used. Four of these allergic rabbits were those injected unsuccessfully in the first series. Although they had received a 3 cc. dose of killed bovine bacilli intratracheally, they had failed to develop any x-ray shadow. A fifth rabbit was one of the hypersensitive controls from the first series that had received saline only. The sixth rabbit, no. 36, was one that had showed the suggestive x-ray shadow last described, which had cleared completely at 7 weeks. Its lungs had been entirely clear for 3 months before being used in this experiment. Immediately before inoculation these rabbits were retested intradermally with 10 mg. of tuberculin, and all of them were found to be hypersensitive.

None of the animals of this series were killed until the disappearance of the shadow was complete, or nearly so. From the autopsies, however, it will be seen that the x-rays often seemed clear before the lungs had returned completely to normal. No autopsies were performed

during the height of the shadows because it was thought that the pathological picture of the active epituberculosis might be complicated by some residuum from the previous experiment in which they had been employed. This series was carried out more for the purpose of following the development and resolution of the shadows by x-ray. Each of these 6 rabbits was injected intratracheally with 4 cc. of an emulsion of killed bovine bacilli, prepared as in the first series. X-rays were taken at intervals of 48 hours, 1, 2, 3, 4, 5, 6, 7, 9, 10 and 14 weeks following the injection. The results are shown in Table II. Again one rabbit (no. 41) failed to show any reaction, and the shadows in the x-ray of no. 33 were too diffuse to be of use. The latter rabbit showed no pathological changes in the lung when killed 5 months after the injection except a slight amount of emphysema. The former rabbit, also killed 5 months after the injection, in spite of its negative x-ray, did show a tiny depressed scar with blebs of emphysema at its right apex, which, microscopically, consisted only of strands of connective tissue between alveoli.

The other 4 rabbits developed the typical localized x-ray shadow, appearing as early as 48 hours after the injection, reaching its maximum density in an average of 4 weeks, and slowly resolving. The complete resolution was delayed in comparison to the results in the first series, traces of the shadow remaining for 3½ months, perhaps because of the larger dose of bacilli used, or perhaps because in these rabbits this was actually a second dose of tuberculoprotein in the same lung.

Rabbit no. 36, killed while a trace of its x-ray shadow remained, first showed a shadow at 1 week following the intratracheal injection of killed bovine bacilli, at which time its shadow already stretched from the hilum of the right lung to its periphery between the 4th and 6th ribs, below which level it reached two-thirds of the way into the lung field. At 2 weeks the shadow was much denser and reached to the pleura between the levels of the 2nd to the 5th interspaces; at 3 weeks, the entire right lung below the level of the 2nd interspace was involved in the shadow, which was not quite so homogeneous as before; at 4 weeks resolution had begun, the upper lobe having cleared down to the level of the 4th rib and the lower area having cleared slightly at its periphery; at 6 weeks this was unchanged, but at 7 weeks there was further peripheral clearing. The lung was almost clear at 10 weeks, showing only a medial shadow below the heart in the right lower lobe. The rabbit was then killed and its lung showed, grossly, a firm area,

TABLE II

RABBIT NUMBER	SENSITIZED WITH	PREVIOUS CONDITION	X-RAY SHADOW					RABBIT KILLED	LESION AT AUTOPSY		
			Site	Character	Time of appearance	Maximum density	Cleared		Gross	Microscopic	Tubercle bacilli
36	R_1	Shadow in Series I; clear for 3 months	Rt. lower	Localized	1 wk.	3 wks.	Shadow almost clear when killed	10 wks.	Organizing pneumonia	Organizing tbc. pneumonia	+
49	H_{37}	No reaction in Series I	Rt. upper	Localized	48 hrs.	4–5 wks.	9 wks.	5 mos.	Scarring	Scarring, dilated bronchioles	0
62	B_1	No reaction in Series I	Rt. upper	Localized	48 hrs.	4–5 wks.	11 wks.	5 mos.	Small wedge-shaped scar	Organizing epithelioid cell pneumonia	+
26	H_{37}	Saline control in Series I	Rt. upper	Localized	48 hrs.	3–6 wks.	14 wks.	5 mos.	Small scars	Small scars	0
33	H_{37}	Diffuse reaction in Series I	Bilateral	Diffuse	2 wks.	2 wks.	7 wks.	5 mos.	Normal	Normal	0
41	R_1	No reaction in Series I	0	—	—	—	—	5 mos.	Slight scarring	Slight scarring	0

Note: 4 cc. killed B_1 injected intratracheally in each rabbit.

measuring 3 x 0.8 mm., in the region of the residual x-ray shadow (Fig. 7). The remainder of the lung tissue, both grossly and microscopically, was normal. Microscopically, the area noted in the right lung showed a dense infiltration of the alveoli and the alveolar walls with epithelioid cells and scattered giant cells and also foci of caseation. In places there was organization about the periphery, radiating strands of connective tissue also extending into the adjacent lung tissue (Fig. 8). Surrounding the area there were large emphysematous alveoli. Tubercle bacilli were still stainable in this area, many of them fragmented. None of the other viscera were tuberculous.

The other 3 rabbits, nos. 26, 49, and 62, were killed 5 months after their intratracheal injection of killed bacilli, and 2 to 3 months later their x-rays indicated that their lungs were clear. Rabbit no. 26, at 48 hours, showed a faint clouding of the right upper lobe. By 2 weeks this was a dense shadow reaching from the apex to the level of the 4th rib and stretching from the root of the lung to its periphery. It was even more dense and homogeneous at 3 weeks, and showed no further change at 4 and 6 weeks. At 7 weeks, there was slight resolution at the periphery, and this had progressed markedly at 10 weeks. At 3½ months, there remained only a slight apical shadow, which in the plate taken at 5 months could barely be seen as a faint blurring. At autopsy, at the extreme apex of the right lung, in the region of the former x-ray shadow, was a depressed scar and several tiny emphysematous blebs. No other lesion was found. Microscopically, there was no suggestion of tuberculosis, only emphysema and scar tissue in the area were noted grossly.

In rabbit no. 49, at 48 hours, a dense shadow projected out from the right root into two-thirds of the pulmonary field. This had spread longitudinally at 1 week, but had not reached the pleura. At 3 weeks, it had spread entirely across the lung from the apex to the level of the 4th rib, below which it reached only half way into the lung field. At 4 to 5 weeks, the entire upper lobe was densely consolidated, as well as the inner half of the lower lobe. At 6 weeks, the lower lobe was virtually clear and the upper lobe was resolving in spotty fashion. Further resolution was noted at 7 weeks, and the lung was clear at 9 weeks. The plate was normal before the killing of the rabbit at 5 months. Again the autopsy showed no remnant of tuberculosis, but, in spite of the negative x-ray, there were blebs of emphysema and scarring about collapsed bronchioles in the region of the previous shadow. Microscopically, foci of lymphoid cells were seen in the scar tissue about the collapsed bronchioles.

Rabbit no. 62 (Figs. 11 through 15), at 48 hours after its intratracheal injection, showed a definite clouding of the right upper lobe. This was located between the 4th and 6th ribs. At 2 weeks, this was a dense, homogeneous consolidation reaching from the apex and extending from the root to the periphery. At 4 weeks this reached down to the level of the 6th rib. There was no change at 5 weeks. At 6 weeks, there was decided clearing at all the borders of the shadow, the residuum of which remained only between the 3rd rib and 6th interspace. There was no alteration at 7 weeks, while at 9 weeks only a spotty shadow remained between

the 3rd and 5th ribs. This persisted at 10 weeks. The x-ray was clear at 11 weeks and was also clear in the plate taken just before killing of the rabbit at 5 months. Again the x-ray failed to reveal residual changes in the lung, for grossly the right lung showed a wedge-shaped scar, 1 cm. wide and 0.8 cm. deep, in the posterior portion of the right upper lobe, surrounded by fairly large blebs of emphysema. Microscopically, this wedge consisted of residual epithelioid cell pneumonia, which was almost completely organized, but in which fragments of tubercle bacilli could still be stained.

In the third series, 23 rabbits were used. Here, not only was an attempt made to study the development and resolution of the x-ray shadow in the allergic animal; to correlate this shadow with its pathological appearance in all its stages; and to contrast it with the reaction caused by a similar injection of living tubercle bacilli, but also, finally, to ascertain the effect of killed bacilli in normal, non-allergic animals, as another control for the series. The results are given in Table III.

Two animals, immunized and sensitized, nos. 71 and 78, were given 4 cc. of a suspension of living bovine tubercle bacilli intratracheally, and 4 cc. of a similar suspension of killed bovine bacilli were injected intratracheally into each of 12 allergic and 9 normal, non-allergic rabbits. X-rays were taken at 48 hours, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 12 weeks following the injection. Unfortunately, 5 allergic animals, as well as 4 previously normal ones that were injected intratracheally with killed bacilli, died from intercurrent pneumonia during the period of the experiment. These animals are eliminated from the present description, although in the allergic ones the development of the typical x-ray shadow had preceded the intercurrent pneumonia and, microscopically, the area of the shadow showed the change characteristic of that in the animals in which no intercurrent infection occurred.

The two immunized, hypersensitive rabbits, nos. 71 and 78, injected with living bacilli, both developed a spreading x-ray lesion. Rabbit no. 78 at 48 hours already showed a shadow in the right lung between the level of the 2nd rib and the 5th interspace stretching from the root to the periphery. This showed no change at 1 week, but at 2 weeks it had spread considerably, its lower margin then reaching almost to the base and its upper level being at the apex. By 3 weeks, there was, in addition, some mottling of the left lung field. There was no further change until 9 weeks, when an oval area of clearing was noted on the right, which

at 10 weeks was obviously a cavity. The rabbit died at 11 weeks after the injection, and autopsy (Fig. 10) revealed extensive areas of caseous pneumonia in both lungs with a large, multilocular cavity with a ragged caseous lining in the right lung. The liver contained a caseous, tuberculous nodule, but none was found in the spleen. Myriads of tubercle bacilli were stained in the involved areas.

Rabbit no. 71 had a more chronic course, living for 6 months. At 48 hours its x-ray showed a shadow in the right lung between the 2nd and 5th ribs which had spread by 2 weeks over most of the right lung field, and at 3 weeks there was also evidence of involvement of the left lung. There was little change in the x-rays until the rabbit's death. At autopsy, the lungs, grossly, showed caseous pneumonia, more extensive in the right than in the left lung, but there was no cavity formation. Microscopically, there was considerable organization about the caseous areas, which, nevertheless, were spreading. Other organs showed scattered caseous foci, always encapsulated.

The 9 normal animals were most interesting. Only one, no. 93, developed a reaction severe enough to produce an x-ray shadow suggestive of epituberculosis. This reached its height in 2 weeks and quickly resolved, its x-ray at 5 weeks being entirely clear. This rabbit was killed at the end of 8 weeks after the injection, and showed macroscopic pleural adhesions and a slightly collapsed area posteriorly at the site of the former shadow in the right lung. Microscopically, there was thickening of the alveolar walls in this region with small discrete nodules of mononuclear and giant-cells, usually peribronchial, in these areas. Tubercle bacilli were stained in these areas. The other organs were normal.

The 7 other normal rabbits, killed at intervals of 30 hours to 8 weeks after the injection, showed a most remarkable paucity of microscopic change. The lungs exhibited, macroscopically, no deviation from normal whatsoever. Their histological picture varied; those killed at the end of 30 hours (Fig. 2) and 1 week, showed small foci of mononuclear-cell pneumonia; later ones revealed small areas of encapsulated mononuclear cells. In no section was any necrosis or caseation found, and the microscopic change was so slight that it was easy to understand why no macroscopic or x-ray change could be found. However, in spite of the slight reaction, acid-fast stains revealed in the 30-hour rabbit myriads of clumped tubercle bacilli in the alveoli associated with the small foci of pneumonia, while in the rabbits killed 1 to 3 weeks and longer after the injection, tubercle bacilli

TABLE III

RABBIT NUMBER	SENSITIZED WITH	INTRATRACHEAL INJECTION 4 CC.	X-RAY SHADOW					TIME OF RABBIT'S DEATH	LESION AT AUTOPSY		
			Site	Character	Appeared	Maximum density	Disappeared		Gross	Microscopic	Tubercle bacilli
78	R_1	Living B_1	Bilateral	Spreading	48 hrs.	3–9 wks.	Persisted	11 wks. (D)*	Caseous pneumonia with cavities	Caseous pneumonia, cavities, some organization	+
71	R_1	Living B_1	Bilateral	Spreading	48 hrs.	3–9 wks.	Persisted	6 mos. (D)	Caseous pneumonia	Organizing caseous pneumonia	+
89	0	Killed B_1	0	—	0	—	—	30 hrs. (D)	0	Small areas of pneumonia with polys. and mononuclear cells	+
95	0	Killed B_1	0	—	0	—	—	1 wk. (K)*	0	Small areas of pneumonia with polys. and mononuclear cells	+
88	0	Killed B_1	0	—	0	—	—	3 wks. (D)	0	0	+
86	0	Killed B_1	0	—	0	—	—	3½ wks. (D)	Oedema	Encapsulated small tubercles	+
85	0	Killed B_1	0	—	0	—	—	5 wks. (K)	0	Encapsulated small tubercles	+
93	0	Killed B_1	Rt. lung	Localized	1 wk.	2 wks.	5 wks.	8 wks. (K)	Adhesions. Atelectasis	Encapsulated small tubercles	+
90	0	Killed B_1	0	—	0	—	—	—	—	—	—
96	0	Killed B_1	0	—	0	—	—	8 wks. (D)	0	Encapsulated small tubercles	+
87	0	Killed B_1	0	—	0	—	—	—	—	—	—

66	R_1	Killed B_1	0	—	0	—	—	48 hrs. (K)	Consolidation	Patchy pneumonia; polys. and monos.	+
81	R_1	Killed B_1	0	—	0	—	—	1 wk. (K)	Small foci of consolidation	Tuberculous pneumonia	+
68	R_1	Killed B_1	Rt. lower	Localized	48 hrs.	Not reached at death	Killed before disappearing	8 days (D)	Consolidation	Tuberculous pneumonia; secondary infection	+
67	R_1	Killed B_1	Rt. upper	Localized	1 wk.	Not reached at death	Killed before disappearing	3 wks. (D)	Consolidation	Tuberculous pneumonia	+
63	R_1	Killed B_1	Rt. upper	Localized	48 hrs.	2–4 wks.	Fading at death	5 wks. (K)	Consolidation	Organizing tuberculous pneumonia	+
72	R_1	Killed B_1	Rt. lung	Localized	48 hrs.	3–4 wks.	Fading at death	7 wks. (D)	Patchy consolidation	Organizing tuberculous pneumonia; secondary infection	+
75	R_1	Killed B_1	Rt. lower	Localized	1 wk.	2–3 wks.	Fading at death	8 wks. (K)	Patchy consolidation	Organizing tuberculous pneumonia	+
79	R_1	Killed B_1	0	—	0	—	—	10 wks. (D)	0	0	0
84	R_1	Killed B_1	Rt. upper	Localized	48 hrs.	2 wks.	8 wks.	13 wks. (K)	Scarring	Scarring, epithelioid cells, localized emphysema, collapsed bronchioles	+
73	R_1	Killed B_1	Rt. upper	Localized	1 wk.	2–4 wks.	9 wks.	5 mos. (D)	Empyema and pyogenic pneumonia		0
82	R_1	Killed B_1	Rt. upper	Localized	2 wks.	2–3 wks.	9 wks.	6½ mos. (K)	Scarring	Scarring	0
74	R_1	Killed B_1	0	—	0	—	—	6½ mos. (K)	Scarring	Scarring	0

* D = died; K = killed.

were stainable in abundance along the lymphatics of the bronchi and alveolar walls and were associated here with small accumulations of well preserved epithelioid cells and giant cells. No lymph node involvement was noted in the gross, but the appropriate stains revealed many tubercle bacilli in the small lymphoid foci about the neighboring bronchi. The difference between this slight reaction of these normal rabbits to the intratracheal injection of the killed bovine tubercle bacilli and the massive reaction of the allergic animals was really overwhelming.

Of the 12 allergic rabbits injected in this series, only 2 failed to show the usual localized x-ray shadow. One of these, no. 74, in spite of a negative x-ray series when killed 6 months after the injection, showed a small macroscopic scar at the posterior lower margin of the right upper lobe; but the other, no. 79, failed to show any gross or microscopic change at its death 10 weeks after the injection; nor were any tubercle bacilli stained in the lungs of either of these rabbits. The maximum density and extent of the shadows developed by the remaining 10 animals was again reached in 2 to 4 weeks, and resolved slowly, taking months to clear.

Rabbit no. 66, killed 48 hours after the injection at which time its x-ray was still clear, showed accumulations of polymorphonuclear and mononuclear cells in the alveoli and many tubercle bacilli (Fig. 1).

Rabbit no. 81, killed at 1 week, also with negative x-rays, showed larger areas of a more definitely tuberculous pneumonia with epithelioid and giant cells, and also many tubercle bacilli in the pneumonic areas.

The rabbits killed later all showed tuberculous pneumonia with definite caseation. Rabbit no. 63 was killed at 5 weeks, having developed an x-ray shadow in the right upper lobe at 48 hours. At 1 week this reached from the root to the periphery between the levels of the 3rd and 5th ribs; at 2 weeks the shadow had spread down to the level of the 8th rib, although it did not reach to the pleura over this entire area. There was no further change at 3 or 4 weeks, but at 5 weeks the shadow was definitely less extensive, its outline having retracted to a wedge similar in shape to that in the 1 week x-ray. At autopsy there was an extensive, irregular area of consolidation (Fig. 5), measuring 4 by 1.5 cm., in the region of the x-ray shadow, which microscopically (Fig. 6) showed encapsulated foci of caseation and a diffuse network of fresh scars. In other areas there are alveoli which obviously contain a resolving exudate, for in many of them there are only small sheets of epithelioid cells or, indeed, only a single epithelioid or giant cell. The walls of some of these alveoli are thickened. Tubercle bacilli are stained here.

Rabbit no. 75 showed no change in its x-ray until 1 week after the intratracheal injection of killed bovine bacilli, at which time the shadow reached across the lung field in the fourth right interspace. At 2 weeks, it reached from the apex to the 7th rib, and at 3 weeks it showed no change; at 4 weeks it had begun to resolve, having cleared somewhat both at the apex and at the periphery, but at 5 weeks its outlines again resembled those of the 3 weeks shadow. The plates taken at 7 weeks were overexposed but, nevertheless, revealed marked clearing. The last plate was made at 8 weeks, just prior to the killing of the rabbit, and it showed a residual homogeneous shadow in the 4th interspace. At autopsy this area presented an organizing pneumonia with residual caseation which seemed rather more extensive than the resolving x-ray shadow had indicated, but which was located in the site of the x-ray shadow.

The x-ray of rabbit no. 84 showed a slight blurring of the right upper lobe at 48 hours. At 1 week there was a definite shadow across the 2nd interspace. This reached its maximum density and extent at 2 weeks, occupying the entire right upper lobe. At 3 and 4 weeks the extreme apex was clear, but the shadow had undergone no other resolution. The plates taken at 5 and 6 weeks were too poor to read and at 7 weeks there was marked peripheral clearing, the shadow then extending only one-third of the way across the lung field. There was only slight mediastinal fuzz at 8 weeks and at 9 weeks the lung seemed clear. Yet when the rabbit was killed at 13 weeks, the lung, grossly (Fig. 9), showed residual depressed scars and emphysema at the site of the former shadow. Microscopically, this was still recognizable as tuberculous, for sheets of epithelioid cells remained in the scar tissue around collapsed and dilated bronchioles. Tubercle bacilli could still be stained in this area, though they were poorly preserved and for the most part fragmented.

Rabbit no. 82 was allowed to live for 6½ months after the intratracheal injection. It showed no x-ray shadow until 2 weeks following the injection, at which time the shadow occupied almost the entire right upper lobe. It showed no change at 3 weeks, but at 4 weeks resolution was under way and the shadow was between the 2nd and 5th right ribs. At 5 weeks its lower border had receded to the level of the 4th rib and at 6 weeks it was much less dense than before. There was little change at 8 weeks, and at 9 weeks the lung appeared clear. At autopsy, this rabbit also showed residual scarring and emphysema at the site of its earlier x-ray shadow.

DISCUSSION

From the foregoing it can be seen that x-ray shadows with a form and course closely resembling those clinically designated as epituberculous in the human being can be produced experimentally by introducing material containing killed tubercle bacilli into a localized area of the bronchial tree of a hypersensitive animal. At first, the slowly developing x-ray shadow produced cannot be differentiated

from that brought about in an immunized, sensitized rabbit in which living bacilli are similarly placed; but after a maximum of 5 weeks, the shadow produced by dead bacilli begins to resolve, whereas that produced by living bacilli continues to spread. With the doses used, the latter rabbit finally dies of a fatal tuberculosis, whereas the pulmonary lesion in the former gradually undergoes complete resolution, leaving, at most, only a slight residue of scar tissue. The normal nonallergic animal reacts in a manner strikingly different from that of the allergic rabbit, in that it fails to develop any marked reaction to the presence of the dead bacilli.

The gradual increase in density and the gradual clearing of the x-ray shadow, often beginning at the periphery, in the hypersensitive rabbits that received dead bacilli conform in all respects to the appearance and course of the x-ray shadows in children with epituberculosis, except that in the former the hilum also clears due to the fact that there are no large hilum nodes. The longer period required for the process to clear in the human being may well be due to the fact that a bronchial erosion permits the continual aspiration of material from the caseous node over a period of time, whereas in the present experiments there was no such opportunity. Furthermore, it is conceivable that the dead tissue represented by the caseous material of the node containing dead bacilli produces a reaction that is more lasting than that caused by dead bacilli alone.

When examined pathologically, the lesion causing the x-ray shadow in the lung of the hypersensitive animal injected wth dead bacilli shows a typical tuberculous pneumonia. Very early there are many polymorphonuclear leucocytes as well as mononuclear cells in the alveoli, but soon only the cells typical of tuberculosis are seen—epithelioid cells, giant cells and lymphocytes. Frequently there is a considerable amount of caseation. In all cases the dead bacilli or their fragments can be stained in the site of the lesion for a period of several months. After 5 weeks, the periphery of the consolidated area shows fibroblasts and beginning organization, and associated with the scarring and removal of the debris of tissue, a loss of some lung substance occurs with a consequent development of foci of emphysema. The loss of tissue, however, is never very great. The biopsy material described by Rubenstein (11), as well as the autopsy

of Eliasberg and Neuland (1) during the process of the disease and that of Grävinghoff (5) a year after the disappearance of the shadow, all fit accurately into this picture and help to support the experimental evidence of the mode of production of epituberculosis offered in this paper as well as the tuberculous nature of the process.

Although, in the presence of enlarged bronchial nodes, atelectasis is always a possible explanation of a pulmonary shadow, and was found by Epstein (7) in combination with tuberculous lesions, it is highly unlikely that atelectasis alone can account for most cases of clinical epituberculosis. The slow process of clearing, the fact that clearing almost always occurs from the periphery inward, both speak against atelectasis as the cause of the condition. However, it is quite possible that some cases of benign pulmonary shadow in children do represent atelectasis caused by the occlusion of a bronchus by an enlarged tuberculous node. That this is the case is illustrated by the report of Morlock and Pinchin (12).

However, for reasons set forth in detail in the beginning of this paper, it is regarded as more probable that most cases of epituberculosis represent instances in which a caseous lymph node containing relatively few viable bacilli discharges its caseous substance, impregnated with tuberculoprotein and the bodies or fragments of bacilli, into a bronchus in an individual who has been sensitized and to some degree immunized by the previous infection. Since in the presence of even very large numbers of living bacilli, the progress of tuberculosis is greatly retarded in the animal immunized by previous infection, as is well illustrated by pertinent animals in the present experiments, it is altogether likely that since, in the human being, the rupture of a caseous node into a bronchus occurs only after infection has been present for a time long enough to establish some degree of acquired resistance, the presence of moderate numbers of living bacilli in the discharged material would not be incompatible with the resolution of the process under the influence of acquired immunity.

Certainly the present experiments demonstrate that the bronchogenic distribution of dead bacilli in the hypersensitive animal can reproduce with remarkable fidelity the development, the course and the resolution, of the x-ray shadow characteristic of epituberculosis.

The discharge of a sufficient amount of material from a caseous

node into a bronchus in an individual sensitized or rendered hypersensitive by the original infection will always produce an area of consolidation which will possess a rather wedge-shaped outline because of the bronchogenic distribution of the material in the lung. What the outcome in such a case will be—whether the area will spread progressively or undergo regression; whether in the case of regression, resolution will occur more rapidly or more slowly; the degree to which a residue of scarring will remain—all of these circumstances will depend upon the amount of material discharged; whether only one discharge occurs, followed by healing over of the bronchial perforation, or whether material continues to be discharged during a period of time; the number of viable bacilli in the material entering the lung, the degree of acquired resistance of the individual; and the degree of hypersensitivity.

SUMMARY

(1) An x-ray lesion, quite like that of so-called epituberculosis, or benign resolving childhood pulmonary tuberculosis, was produced experimentally by introducing dead tubercle bacilli into the bronchus in hypersensitive rabbits. This shadow, which exhibited the form and clinical course of that in human epituberculosis, reached its maximum density in 2 to 4 weeks, and then gradually cleared completely, clearing often beginning at the periphery, as is common in the case of the shadow of epituberculosis.

(2) No similar x-ray shadow occurred in non-allergic animals subjected to the same procedure.

(3) Immunized, hypersensitive animals injected intratracheally with living tubercle bacilli developed a similar shadow which, however, spread progressively to a fatal termination.

(4) The macroscopic appearance of this epituberculosis-like shadow, studied at different intervals, was that of a tuberculous pneumonia which clears by resolution and organization. After resolution, strands of non-specific scar tissue may be found at the site.

(5) Histologically, the lesion produced is that of a typical tuberculous pneumonia with epithelioid and giant cells, lymphocytes and caseation. Tubercle bacilli or their fragments could be stained as

long as the reaction remained. Later, peripheral organization, absorption of the exudate and non-specific scar formation occurred.

(6) These findings demonstrate that the peculiar characteristics of epituberculosis can be reproduced by the discharge of dead bacilli into the lung of an allergic individual by way of a bronchus. On the basis of this fact, together with certain considerations discussed in the body of this paper, it is suggested that characteristic epituberculosis represents in many, if not in all, cases the result of erosion of a bronchus by a caseous lymph node containing relatively few viable bacilli; and that the characteristic shadow represents a tuberculous pneumonia produced by the discharge of caseous material impregnated with tuberculoprotein and dead bacilli, though containing some living bacilli, into the lung of a body sensitized and immunized by the previous infection. If a similar accident occurs in the case of a node teeming with live bacilli, a shadow of precisely similar form will develop, but the process will extend progressively. The various and clinically familiar shades between the benign retrogressive wedge-shaped area of epituberculosis, and the wedge-shaped rapidly progressive area of active tuberculosis, may be expected to occur depending upon the balance between the number of viable bacilli in the discharging node, and the degree of acquired resistance and hypersensitivity of the body.

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EXPLANATION OF ILLUSTRATIONS

(Photographs and x-rays by Mr. Milton Kougl)

PLATE 1

FIG. 1. Lesion in allergic rabbit no. 66, 48 hours after intratracheal injection of killed bovine tubercle bacilli. Magnification ×1.5, showing size of area of consolidation.

FIG. 2. Control rabbit no. 89, non-allergic, showing absence of any gross reaction 30 hours after intratracheal injection of killed bacilli. Acid-fast stains, however, revealed myriads of bacilli in this area. The dark areas at the periphery of the lung are foci of pulmonary oedema.

FIG. 3. Lesion in allergic rabbit no. 40, 3 weeks after intratracheal injection of killed bovine bacilli.

FIG. 4. Photomicrograph (magnification ×90) of lesion shown in Fig. 3, showing area of tuberculous pneumonia with caseation.

FIG. 5. Lesion in allergic rabbit no. 63, 5 weeks after intratracheal injection of killed bacilli.

FIG. 6. Higher magnification of lesion in Fig. 5, showing organization of tuberculous pneumonia.

FIG. 7. Contracting area of organizing pneumonia in allergic rabbit no. 36, 10 weeks following intratracheal injection of killed bacilli.

FIG. 8. Edge of lesion in Fig. 7, showing scarring surrounded by emphysematous alveoli.

FIG. 9. Wedge-shaped scar in allergic rabbit no. 84, 3 months after intratracheal injection of killed bacilli.

FIG. 10. Caseous pneumonia with cavity formation in allergic rabbit no. 78, whose death occurred 11 weeks after intratracheal injection of living bovine tubercle bacilli.

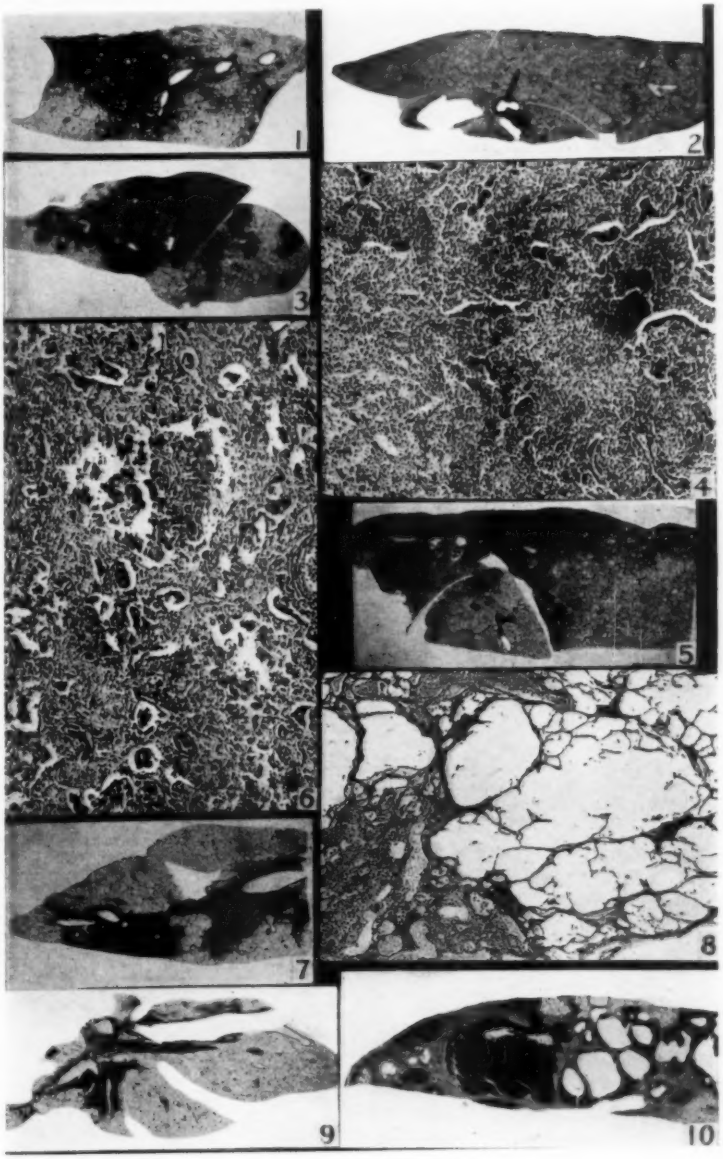

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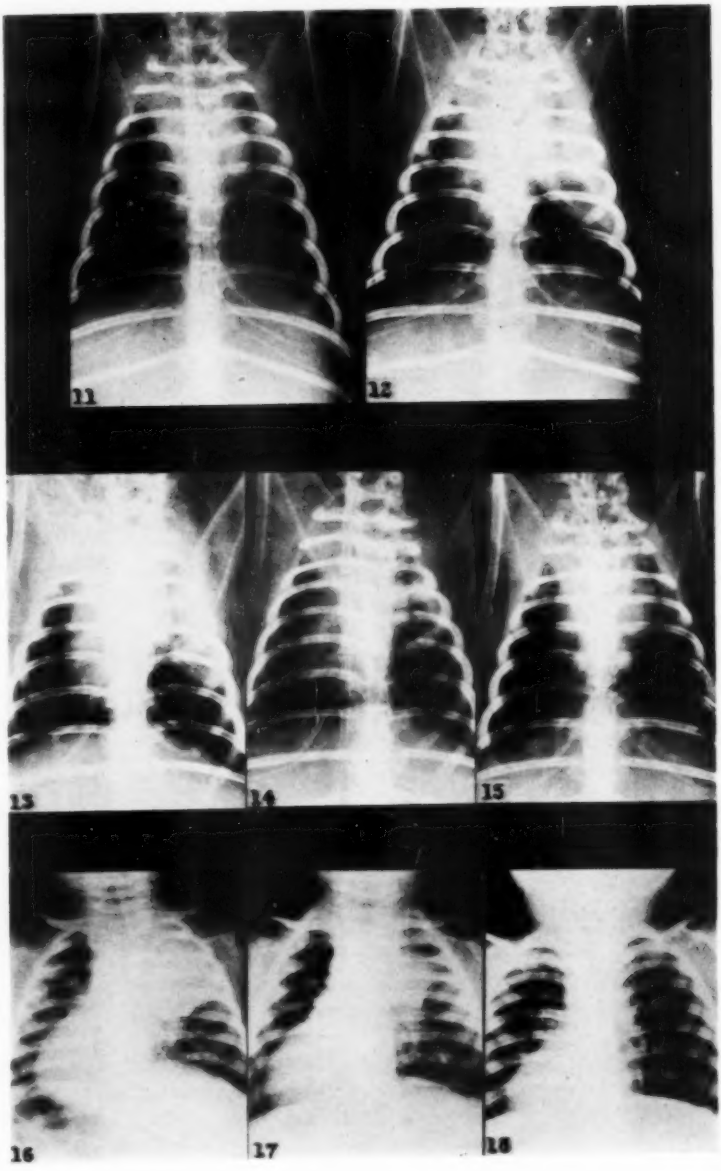
PLATE 2

FIGS. 11, 12, 13, 14, 15. X-ray series of allergic rabbit no. 62, taken at 48 hours, 4, 6, 9 weeks and 5 months, respectively, following the intratracheal injection of killed bovine bacilli. Fig. 11 (48 hours) shows clouding of the right upper lobe. Fig. 12 (4 weeks) shows the lesion at its height; Fig. 13 (6 weeks) shows some clearing at the margins; Fig. 14 (9 weeks) shows a residual spotty shadow between the level of the 3rd and 5th ribs; and Fig. 15 (5 months) shows complete resolution of the shadow.

FIGS. 16, 17, 18. X-ray series of 5½ months old child with epituberculosis from the Tuberculosis Clinic of the Harriet Lane Hospital. Fig. 16 shows the lesion at its height; Fig. 17, taken 2 months later, shows marked clearing; Fig. 18 (taken 1½ years after onset) shows complete disappearance of the pulmonary shadow.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STUDIES ON THE ADRENAL

X. Experimental Studies on Replacement Therapy in Adrenal Insufficiency[1]

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Submitted for publication August 17, 1935

The optimism of the early reports of successful treatment in Addison's disease with extracts of the adrenal cortex has not been sustained by subsequent work. So unsatisfactory, in fact, have been the results in many cases that the question has been raised as to whether the clinical manifestations of Addison's disease are to be attributed solely to dysfunction of the adrenal cortex. Thus the pituitary gland (1) and the adrenal medulla (2) have been suggested as playing a part in producing the syndrome. We have demonstrated the existence of a secondary pituitary insufficiency in animals maintained over long periods in a state of chronic adrenal insufficiency (3). In man also long continued adrenal insufficiency may be expected to induce certain changes; for example, stunting of growth and abeyance of reproductive functions. However, the chief symptoms of adrenal insufficiency as observed in man—anorexia, asthenia, weakness, and so on—are identical with those observed in acute adrenal insufficiency in animals. Since these symptoms in experimental animals are completely remedied by adequate treatment with the adrenal cortex hormone, there is every reason to anticipate no less satisfactory results in man. Although a crisis in Addison's disease may be initiated (4) by dehydration and loss of sodium chloride from the body, the remedial effects following administration of fluids and so-

[1] Read before the Section on Pharmacology and Therapeutics at the joint meeting of the American and Canadian Medical Associations, Atlantic City, June, 1935.

[2] Aided by grants from the Ella Sachs Plotz Foundation and the Hartley Corporation.

dium chloride are only temporary, and like other useful forms of adjuvant therapy these are incapable of supplying the need for the adrenal cortex hormone.

Addison's disease is noteworthy for the great number of methods which have been reported as curative of the condition. Addison (5) mentions the case of a patient who was ostensibly cured by drinking large quantities of brandy. Subsequent writers (5) report cures with desiccated adrenals, fresh adrenals, glandular extracts, epinephrine, and so forth. These supposed cures, to which may be added many of recent years, illustrate the possibilities of error in estimating the value of a given treatment by purely clinical observation. Moreover, the chronicity of Addison's disease and its tendency to undergo spontaneous remissions render favorable reports based on immediate results open to question. The ability to maintain life in adrenalectomized animals for extended periods is, therefore, essential before we can accept a given method of treatment as offering a possible replacement therapy for adrenal insufficiency in man.

Our experiments with the commercially available adrenal cortex preparations have demonstrated their utter inability to maintain life in adrenalectomized animals. It is not surprising, therefore, that their clinical application has been unsatisfactory.

COMMERCIALLY AVAILABLE PREPARATIONS

The commercial preparations of the adrenal cortex hormone hitherto available consisted of (1) dried preparations of glands, (2) glycerine extracts for oral use, and (3) extracts prepared for parenteral administration. We have found the first two types of preparations to be utterly devoid of any activity when tested by direct feeding to adrenalectomized month-old rats. This method of assay (6) has proved most satisfactory and is capable of detecting far smaller quantities of the hormone than could conceivably be of any therapeutic use to man. The absence of any detectable amount of hormone in the above described commercial preparations is not surprising when we consider the rapidity with which the hormone is destroyed (7) and the small concentration of it actually present even in the fresh glands. Even under ideal conditions of preservation it requires several hundred grams of beef glands per day to maintain life in an adrenalectomized

dog (8). Administration of a few grams of dried glands, in which the hormone, originally present, has for the most part been destroyed by autolytic processes, cannot, therefore, offer the slightest prospect of supplying an appreciable amount of adrenal cortex hormone.

Our experiments (6) with the commercially available extract prepared by the method of Swingle and Pfiffner also failed to corroborate the claims made for this extract. Thus, an extract labelled as possessing a potency of 20 dog units per cubic centimeter was found to contain less than one rat unit per cubic centimeter. This finding is in accord with the recent experiments of Rogoff (9).

NEW PREPARATIONS SUITABLE FOR ORAL THERAPY

The parenteral administration of any therapeutic agent suffers from the disadvantage that it necessitates the preparation of a highly purified product. The presence of toxic impurities may easily mask the beneficial effects of any hormone present in a given extract. Thus, in an experiment in which an incompletely purified extract was administered intraperitoneally to adrenalectomized rats, doses of one cubic centimeter per rat per day failed to provide complete replacement therapy. The same extract administered orally mixed with the animals' food served as a complete replacement therapy in doses as small as 0.05 cubic centimeter. The noxious impurities present in this extract when given by mouth were without deleterious effects.

Another important advantage favoring oral therapy in administering the adrenal cortex hormone is the fact that this hormone is much more effective when administered in multiple doses than when an equal amount is given in a single dose. This advantage of divided doses at frequent intervals is practical only when the drug is given by mouth.

We (7) have recently reported a simple method for concentrating the adrenal cortex hormone in a form suitable for oral administration. Activated charcoal effectively adsorbs the hormone from aqueous solution. One gram of the charcoal removes the hormone from 300 grams of glands (7) and thus effects a high concentration of the hormone. It is thus only necessary to extract the glands with acetone, remove the acetone, and agitate the aqueous residue with char-

coal to remove over 95 per cent of the hormone present in the glandular material. To get rid of the impurities incidentally adsorbed on the charcoal, the adsorption product is washed with dilute alkali (sodium hydroxide or ammonia), hydrochloric acid and ethyl alcohol, respectively. The alkali removes phenolic decomposition products; the acid elutes epinephrine; and the alcohol dissolves certain lipoidal impurities incidentally adsorbed on the charcoal.

The adrenal cortex hormone is rapidly destroyed (probably by autolytic processes) when the adrenal glands are removed from the animal body. The hormone is quite stable, however, in the form of its charcoal adsorbate. Thus, a preparation assayed at monthly intervals was found to undergo no detectable deterioration over a period of six months when left exposed to room temperature and in contact with the air.

The charcoal adsorbate of the hormone has been found (7) capable of maintaining life in adrenalectomized rats and dogs, the hormone being eluted in the gastro-intestinal tract from its combination with the charcoal. The greater effectiveness of feeding the adsorption compound as compared with parenteral injection of an extract is probably due to the slow elution of the hormone from the charcoal and its gradual absorption from the alimentary tract (10).

When large amounts of the charcoal adsorbate are administered, the efficiency of the hormone is reduced, probably because of its incomplete elution in its passage through the gastro-intestinal tract. To overcome this loss of activity the hormone should be eluted from the charcoal and administered uncombined. This elution may be satisfactorily accomplished by the following procedure: The charcoal-hormone combination is suspended in three to five times its volume of chloroform. After several hours the chloroform is removed through a Buchner funnel and the process repeated six times. The chloroform is removed by distillation *in vacuo*, leaving a brownish resin soluble in aqueous ethyl alcohol. This alcoholic solution may be administered directly, or the resin may be dissolved in alcohol and incorporated with sodium chloride, lactose, starch, or other suitable carrier and given in capsules or compressed tablets.

The use of the product just described avoids the necessity of administering large amounts of inert charcoal. When relatively small

amounts of the hormone are to be given, the charcoal combination should prove adequate. When large doses of hormone are necessary, however, the use of excessive amounts of charcoal would be inefficient and undesirable, and in these cases the oral administration of the eluted hormone is preferable.[3]

DOSAGE

So far no investigation of the dose of the adrenal cortex hormone required by man has been recorded. This must obviously be a variable, depending upon the severity of the adrenal insufficiency in

TABLE 1

The adrenal cortex hormone requirement in various animal species

ANIMAL SPECIES	NUMBER OF ANIMALS	WEIGHT IN KILOGRAMS	SURFACE AREA IN SQUARE METERS	RAT UNITS OF HORMONE NECESSARY PER DAY FOLLOWING ADRENALECTOMY	RAT UNITS PER SQUARE METER OF BODY SURFACE PER DAY
Mouse*	6	0.02	0.0084	1.0	120
Rat	10	0.25	0.036	3.5	97
Cat	3	2.0	0.16	20	125
Dog	6	8.4	0.46	55	120
Man†	—	60.0	1.89	220†	—

* The results on mice are based on unpublished data of Dr. Evelyn Howard.

† The value for man is estimated from the data obtained on the experimental animals, assuming the human requirement to be proportional to the surface area.

any given patient. For practical purposes, however, it is essential to know approximately the amount of hormone necessary to supply the needs of an individual. This value may be derived indirectly from the data of Table 1, and is based on the hormone requirement of adult adrenalectomized mice, rats, cats, and dogs. The fourth column of the table records the average surface area of the animals studied as calculated from their body weight, using Rubner's (11) data for the value of the constant in Meeh's formula. The fifth column gives the average dose of the hormone necessary to maintain life in the adrenalectomized animals, expressed in terms of rat units. The rat

[3] We are indebted to Merck and Co., Rahway, N. J., for a supply of some of the hormone used in the present investigation, and to Mr. Robert L. Fox, of Greenwald's, Inc., Baltimore, for generous supplies of adrenal glands.

unit as we have defined it (6, 8) is the amount of hormone necessary to maintain normal growth in a 30 day old adrenalectomized rat. The requirement for maintaining growth in a young animal as compared with that for maintaining life in an adult of the same species is out of all proportion to their relative weights. Thus, whereas 1 rat unit is necessary for maintaining growth in an immature rat weighing 30 grams, it requires only $3\frac{1}{2}$ rat units to maintain life in an adult rat weighing 250 grams. Likewise, the requirement for maintaining growth in a 1 kilogram puppy was found to exceed the average dose necessary for maintaining life in adult dogs weighing 5 to 15 kilograms.

The last column of Table 1 shows that the adrenal cortex requirement of mice, rats, cats, and dogs is roughly proportional to their surface areas. The constancy of the proportionality factor is remarkable when we consider the wide individual variations that one encounters in different animals of the same species. Since the surface area is roughly proportional to the active mass of an individual and to his metabolism (11), it is not inconsistent that the adrenal cortex hormone requirement should also be proportional to this body function. If we assume the validity of this proportionality, the data on mice, rats, cats, and dogs permit us to estimate the human requirement as being about 220 rat units per day. This amount will probably seldom be necessary clinically, since the diseased individual, unlike the experimental animal, still possesses some residual adrenal function.

One rat unit, as defined by us, corresponds to the hormone content of 10 to 30 grams of whole beef adrenal glands, depending upon the freshness of the glandular material. We thus see that a relatively large amount of glandular material is necessary for obtaining a sufficient amount of the hormone to be effective therapeutically. The phenolic decomposition products of epinephrine are exceedingly toxic, and since these are present in large quantity in even relatively fresh adrenal glands, their removal is of the utmost importance.

In our experiments we have never encountered any evidence of overdosage. The claims that the hormone produces changes in the functional activity of the reproductive system have been shown (13) to be erroneous, nor have we been able to detect any effect on the

blood sugar or on the blood pressure due to overdosage. Such effects as have been described must be attributed to the presence of impurities in the extracts employed by previous workers. The adrenal cortex hormone, as judged from preliminary studies of its chemical nature, is of relatively small molecular weight, and any excess in the body is probably rapidly destroyed or excreted in the urine (12). There exists no evidence, therefore, to indicate any danger of overdosage with the adrenal cortex hormone. As long as the hormone is administered orally, the danger of toxic effects from slight amounts of epinephrine or other impurities is also minimized. For parenteral administration, only highly purified extracts, free from phenol derivatives, epinephrine, histamine, choline, and extraneous lipoids, should be employed. Except in severe crises or where oral therapy is impossible, frequent divided doses given orally should furnish all the requirements of the organism for the adrenal cortex hormone.

CONCLUSIONS

The adrenal cortex hormone has been prepared in two forms suitable for oral therapy. The combination of the hormone with charcoal is recommended where small doses are indicated. For more intensive treatment the hormone is eluted from the charcoal and administered in solution, tablet, or capsule form. Experiments on the survival of adrenalectomized animals under different forms of therapy have demonstrated the impotence of the various marketed forms of adrenal preparations—dried glands, glycerine extracts, and extracts for injection. This impotence accounts, we believe, for the unsatisfactory results which have been observed clinically in adrenal cortex therapy. The normal human requirement of the adrenal cortex hormone has been calculated from the results obtained on mice, rats, cats, and dogs. There is no evidence of any dangerous results from overdosage. The use of impure preparations, orally or parenterally, however, may give rise to serious toxic symptoms.

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ACUTE STAPHYLOCOCCAL INFECTION OF THE JEJUNUM AND ILEUM

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Received for publication August 14, 1935

The clinical characteristics of acute staphylococcal food poisoning have been made familiar in recent years by the papers of Barber (1) Dack (2), Jordan and associates (3), (4), (5), (6), Ramsey and Tracey (7), Tanner (8), McBurney (9), and Litterer (10). The symptoms appear quickly, and within two to three hours salivation, nausea and vomiting, abdominal pain and diarrhoea, chilliness and prostration may all be present. Repeated experiments have demonstrated that these symptoms may be reproduced in man by the ingestion of sterile broth filtrates of cultures of staphylococci isolated from infected food, and it has been shown, too, that "enterotoxin" may be produced by a variety of strains of the staphylococcus aureus and albus (6). Although Dolman concluded from his experiments that only occasional strains produced "enterotoxin" (11), Borthwick's work brought out the fact that sterile filtrates obtained from cultures of a given strain of the staphylococcus caused necrosis of tissue and haemorrhage in the stomach and duodenum of animals only after the contents of the stomach were adjusted to pH 7.3 (12). It is evident, therefore, that under certain circumstances clinical symptoms may be produced in man and anatomical lesions developed in the gastrointestinal tract of animals by means of toxic filtrates alone. Litterer, however, investigated an epidemic of staphylococcal food poisoning, and demonstrated that viable organisms could be obtained from the stomach contents of some of the affected individuals (10). It appears that no fatal cases have been reported, and little is known concerning the character and extent of the lesions which may be caused by staphylococcal infection of the intestine. No efforts were made in the following case to discover the original source of the infection, but

the history suggests acute food poisoning, and at autopsy extraordinary numbers of staphylococci were found at the site of very extensive diffuse lesions in the jejunum and ileum.[1]

Case History: H. L. H. No. 88858. L. D., a colored girl, 12 years old, was admitted to the Johns Hopkins Hospital on December 1st, 1934, and died about an hour and a half later.

The child had been well until Thanksgiving Day, November 29th, when she ate a very large dinner in the evening, including chicken, vegetables, ice cream, cake and candy. Later on, at another household, she ate again before going to bed at 10:30 p.m. Five hours later she began to vomit, was feverish, and had headache. Vomiting continued throughout the day, and nothing could be retained. She began to have diarrhoea, and was found unconscious on the morning of December 1st, about twenty-four hours after the onset of symptoms.

On admission to the hospital early in the afternoon, the child was comatose. The temperature was 103.4°F. The pulse was rapid, 130 beats per minute, and the respirations were rapid, deep, and labored. There were vague twitching movements of the mouth and upper extremities. The eyes were intermittently crossed, and there was slight rapid vertical nystagmus. A fine tremor of the iris (hippus) was noticed. The extremities were slightly spastic, and the neck was a little stiff on anterior flexion. The spinal fluid was negative (Pancy, 0; cells, 3), and the urine normal except for a trace of acetone. A blood culture was made, and proved positive for haemolytic Staphylococcus albus. Stimulants and intravenous fluids were given, but the child died shortly after admission, about thirty-six hours after the first symptoms had appeared.

Autopsy No. 13966. Anatomical Diagnosis: Acute diffuse enteritis affecting the jejunum and ileum (Staphylococcus albus); "diphtheritic membranes," moulds of jejunum and ileum, in contents of intestines; septicaemia (Staphylococcus albus); thrombi in small vessels of intestine, liver, lung, kidney, vagina, and lymph nodes; focal necroses in liver, spleen, and bone-marrow; small haemorrhages in stomach, colon, vagina, brain and meninges; dilatation of heart; slight ascites; chronic vaginitis.

The body is that of a very well nourished, well developed colored girl, 12 years old. No external lesions are found. The abdominal cavity contains about 200 cc. of clear fluid. The lungs are normal in appearance. The heart is not enlarged, but the ventricles are distinctly dilated. The spleen is a little enlarged, with tense capsule and rounded margins. The stomach contains bile-stained fluid. It shows no gross lesions.

Intestines: The duodenum is normal. The first part of the jejunum shows no lesions for a distance of a few centimetres. Throughout the remainder of the

[1] Rigdon (13) recently described similar lesions produced in the intestine of animals by intravenous injection of staphylococcal toxin.

small intestine and in the colon there is a thin grayish-red, blood-stained fluid in which a dozen or more long, narrow, elastic and friable membranes are found, resembling moulds of the mucosa of the jejunum and upper ileum. Each of these measures 10 to 15 x 1 to 1.5 cm., and shows closely set, parallel, circular ridges corresponding in appearance to folds of the mucosa.

The wall of the jejunum and upper ileum feels indurated, and seems thicker than normal. The entire inner surface looks dull and opaque, and appears to be more coarsely granular than normal. This change is uniform and diffuse. The folds of mucosa in the jejunum and upper ileum are preserved for the most part, and show the normal arrangement, but they are thick and project stiffly. In the lower part of the ileum the folds tend to flatten out and the wall of the intestine is thinner. No definite ulcers are recognized in the gross specimen. Scattered on the inner surface of the small intestine and in the colon are a number of red patches, a few millimetres in diameter, which suggest superficial haemorrhages. Aside from these haemorrhages the colon looks practicallly normal.

The brain and other organs: No gross lesions are recognized in the brain, and the other organs look normal.

Bacterial Cultures: At autopsy, material was taken from the small intestine for culture, and was placed in various media, including those suited especially for the growth of typhoid and dysentery bacilli. No Gram-negative organisms, however, could be grown on any of the media. Even colon bacilli failed to grow.

Staphylococci were present in the contents of the small intestine in extraordinary numbers. A few cubic centimetres of the intestinal contents were placed in 5 cc. of plain broth, and one loop-full of the diluted material was transferred to another tube containing 5 cc. of broth. One loop-full of broth from this second tube was streaked on a plate of plain pork infusion agar. Two hundred colonies of Staphylococcus albus grew on the original plate, which contained, in addition, only a few colonies of Alpha streptococci.

Microscopical Sections: Jejunum: Sections made from various levels show diffuse lesions which are similar throughout the jejunum. Most of the epithelial cells of the villi and glands of the mucosa have been destroyed and have disappeared. Remnants of glandular epithelium are found in the depths of a few crypts. Some of these remaining cells are well preserved, some are necrotic, and there are a few regenerating cells which show mitotic figures. Most of the villi project *in situ* without any epithelial covering, and show evidence of intense damage and diffuse acute inflammation. Many capillaries in the stroma of the mucosa are dilated, and some are filled with thrombi. The tissue of the mucosa is infiltrated with fluid and contains many leukocytes. Many of the tissue cells and leukocytes are necrotic and their nuclei are fragmented. The fibres of the stroma and the walls of blood vessels are intact for the most part. There are small scattered haemorrhages, however, and the distal portions of adjacent groups of villi here and there have disappeared in a good many areas, leaving small superficial ragged ulcers which occasionally extend nearly to the level of the muscularis mucosae.

The ends of such villi are found microscopically as necrotic fragments of tissue in the casts to be described below. The muscularis mucosae and the submucosa are also infiltrated with fluid and leukocytes. In these locations many of the leukocytes are polymorphonuclear cells, but mononuclear phagocytes and many lymphocytes are also present. The walls of some of the small arterioles in the submucosa show hyaline necrosis, and there are fresh thrombi in many of the small veins. There is but slight evidence of inflammation in the muscularis and serosa. In sections stained for bacteria numerous large Gram-positive cocci are found in the glandular crypts and in the mucosa of the jejunum. In places they occur in clumps, or may be found diffusely scattered in other areas. *Ileum:* In the upper third or more of the ileum microscopical changes are found, which are practically identical with those in the jejunum, although they are a little less intense in character. The lesions gradually diminish in intensity in the middle and lower parts of the ileum, and near the ileocaecal valve very little acute inflammatory exudate can be recognized in the tissues. At this level, however, numerous clumps of large Gram-positive cocci are found in the mucus which covers and surrounds the villi and fills the glands of the mucosa. *Colon:* The blood vessels of the mucosa and submucosa are dilated. There are a few small haemorrhages in the mucosa, and necrotic epithelial cells and new cells with mitotic figures can be found lining some of the glands. *Lymphoid follicles of intestine:* Wherever these appear in the sections of intestine, the lymphoid cells appear to be increased in number and the follicles are larger than normal. In the germinal centres there are many necrotic cells and fragmented nuclei. *Casts of Intestinal Mucosa:* These are composed of fibrinopurulent exudate and bacteria, together with scattered fragments of necrotic intestinal villi. Numerous polymorphonuclear leukocytes remain intact, but many of the cells are necrotic and there is marked fragmentation and pyknosis of the nuclei. The casts are everywhere permeated with large Gram-positive cocci which are evidently Staphylococci, and in many places there are very numerous large colonies.

Other Organs: The microscopical sections show a few small haemorrhages in the mucosa of the stomach, in the meninges, and about small blood vessels in the cerebral cortex and floor of the third ventricle. There is distinct hyperplasia of abdominal and axillary lymph nodes, and the germinal centres show some necrotic cells. The sinuses of the lymph nodes are filled with a variety of leukocytes, and there are small thrombi in a few of the peripheral lymph sinuses. In the liver, fresh thrombi are found in numerous small portal vessels. The periportal tissues are infiltrated with small lymphocytes in moderate numbers, and occasional small foci of necrotic liver cells are found. A section of marrow from one vertebra shows a few small circumscribed focal necroses composed of coagulated material, a few leukocytes, and fragmented nuclei. Scattered throughout the spleen are rather numerous irregular foci resembling those in the marrow. The lesions in the spleen are larger, however, and contain abundant fibrin and a few staphylococci. No bacteria can be stained in the focal lesions in the liver and marrow. The kidneys show cloudy swelling of the epithelial cells, and one can find thrombi

in occasional glomerular capillaries. The tissues beneath the epithelial lining of the vagina are infiltrated with numerous lymphoid cells, suggesting a chronic vaginitis. Some of the small veins are filled with fresh thrombi, and there are haemorrhages about these vessels.

SUMMARY

An example of staphylococcal infection of the small intestine is described which gave rise to septicaemia and was fatal within approximately thirty-six hours from the onset of symptoms. The early symptoms were like those of staphylococcal food poisoning, and consisted of nausea, vomiting, diarrhoea and prostration. Later, with septicaemia and circulatory failure, coma and various other neurological signs appeared.

The autopsy showed widespread lesions of unusual character in the jejunum and upper portion of the ileum. The intestinal contents were blood-stained, and included long moulds of the mucosa which were composed of necrotic fragments of intestinal villi, fibrinopurulent exudate, and staphylococci in large numbers. The microscopical sections showed diffuse superficial necrosis and acute inflammation of the mucosa of the jejunum and portion of the ileum affected, associated with numerous staphylococci in the inflamed tissues. Thrombi in small vessels were found in a number of organs, and were most numerous in the jejunum, ileum and liver. There were focal necroses in the liver, spleen and bone-marrow, and small haemorrhages, not associated with thrombi in blood vessels, were scattered in the brain and meninges.

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EXPLANATION OF PLATE

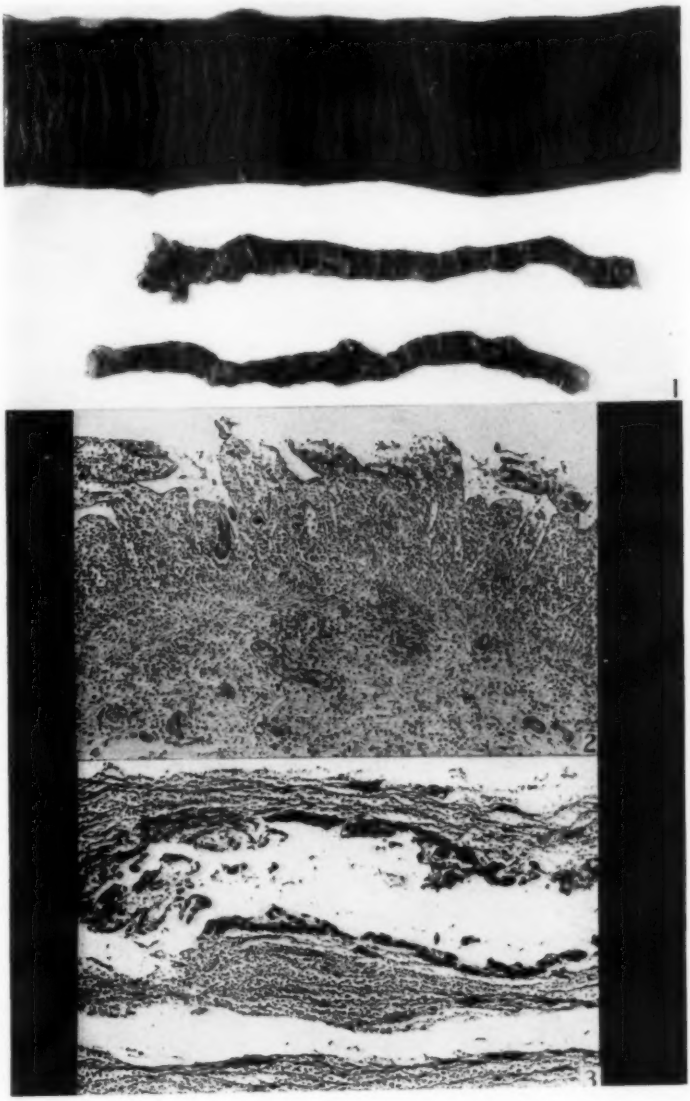
(Photographs by Mr. Milton Kougl)

(Autopsy No. 13966)

FIG. 1 shows numerous haemorrhages in the wall of the jejunum. The widespread superficial necrosis of tissue, found microscopically, is suggested in the photograph by the coarse granular appearance of the surface. This can be seen very well with the aid of a hand lens. Two of the intestinal casts, with ridges corresponding to the architecture of the small intestine, are also shown in Fig. 1 below the jejunum.

FIG. 2. The mucosa and submucosa of the jejunum are diffusely inflamed. Most of the epithelium has disappeared, and there are superficial, ragged, ulcers produced by the sloughing of necrotic villi.

FIG. 3. Bacterial stain of a microscopical section of one of the intestinal casts. The fibrinopurulent character of the cast can be seen. and masses of bacteria are shown in the photograph as solid black clumps.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EPIDEMIC MENINGOCOCCUS MENINGITIS

An Analysis of Twenty-six Cases, Twenty-one of which Occurred in the Spring of 1935

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Submitted for publication September 5, 1935

Between January 1 and May 10, 1935, 21 patients suffering from acute meningococcus meningitis were admitted to the Medical Service of the Johns Hopkins Hospital. In the four years previous to 1935, five cases of cerebrospinal fever had been treated in the Medical Service. The recent sharp increase in the number of hospital admissions due to meningitis is accounted for by the higher general incidence of the disease in the early months of 1935 as reflected in the U. S. Public Health Reports. A larger number of cases was reported in the first part of this year than in a similar period of the preceding four years. The increase applied not only to the country as a whole, but was especially marked in certain sections, among which were the Middle and South Atlantic States. The patients treated in the hospital came from Maryland and the neighboring states and were representative of the disease in the recent regional outbreak.

It is the purpose of the present paper to describe certain features of the illness, as it occurred in these patients, with respect to mode of onset, clinical course, complications, and laboratory findings, and also to relate in some detail the therapeutic use of antimeningococcus serum which appears to have been unusually successful in this small group. The data to be analyzed were derived from the records of 26 patients. Of these, 21 were seen in 1935 and will receive special consideration. Five sporadic cases belonging to the previous four years will be referred to briefly.

With respect to *contagiousness* in the 1935 cases, it is interesting to note that five of the patients gave a definite history of recent close contact with some case of meningococcus meningitis. Furthermore,

two other patients came from a camp for transient unemployed, where cases of meningitis were continually occurring and where, in the barracks, close exposure was possible. The high incidence of known or probable contact infection (33.3 per cent) is of interest in view of the low attack rate for the population as a whole. No data are available concerning the number of meningococcus carriers among the population, but an increase above the normal (2 per cent) might be expected in view of the association between increased incidence of meningitis and rise in the number of meningococcus carriers (1).

The *ages* of the patients ranged from 3 to 52 years. The children, who were admitted, came to the Medical Service because, at the time of their arrival at the hospital, there were no available beds in the Pediatric Service. According to decades of life, 7 were in the first, 5 in the second, 5 in the third, 1 in the fourth, 2 in the fifth, and 1 in the sixth. That the majority of our patients were less than thirty years of age, is in accordance with the well recognized fact that meningococcus meningitis is more liable to occur in the earlier years of life.

The incidence was approximately equally divided between males and females, and between the white and colored races.

With the exception of mild upper respiratory infections, which in some instances preceded the meningitis and to which subsequent reference will be made, all of the patients had been in excellent general health up to the time of onset. In no instance was the meningitis superimposed upon any chronic debilitating illness.

MODE OF ONSET

Among the patients to be described, there appeared to be three, rather well defined, types of onset, two of which emphasize primary involvement of the upper respiratory tract.

Brief accounts of the histories of representative cases illustrate the probable nature of the beginning of the infection.

1. Cases with mild upper respiratory infection of one to three weeks' duration before evidence of meningitis.

C. S. (No. 4, Table I). About three weeks before admission, the patient "caught cold," developed a slight cough and a nasal discharge. There was some abdominal pain and loss of appetite. After continuing at school for one week, she complained that her neck was stiff and that her eyes were sore. These conditions improved under local treatment at home, and attendance at school was not interrupted until two days before admission to the hospital. About that time the abdominal pain became more severe and vomiting occurred. These symptoms were soon followed by pain in the eyes and knees, and finally, just before admission, stiffness of the neck developed.

M. K. (No. 21, Table I). For two to three weeks before admission the patient had had headache, malaise, rhinitis and cough. The condition was not, however, severe enough to require her to remain in bed. One week before admission, pain in the abdomen and legs developed and there was nausea with vomiting, and fever. On admission there were no signs of meningitis. There was no skin rash. There was a widespread herpetic eruption around the lips and nose, and in the mouth and throat. There was pain in the knee-joints without demonstrable abnormalities. A few scattered râles were heard in the chest. The first impression was that the patient was suffering from an acute respiratory infection. Thirty-six hours later she developed a stiff neck and a positive Kernig sign. Lumbar puncture was done which revealed the presence of meningococcus meningitis.

The data just presented exemplify a type of history given by six of the patients. This was characterized by symptoms referable to a mild infection of the respiratory tract of relatively long duration before the appearance of frank meningitis. The importance of infection of the nose and throat as the initial expression of meningococcus infection and as indicating the portal of entry of the disease has been emphasized by Dopter (2) and reaffirmed by others. In Dopter's opinion the rhino-pharyngitis represents the primary meningococcus infection and the subsequent manifestations are "complications" of the infection of the throat. In view of the fact that our patients became ill during January, February, and March, a time of high incidence of respiratory infections not due to meningococci, it is impossible to state whether they suffered from the beginning of the manifestations of a "cold" with meningococcus rhino-pharyngitis, or acquired invasive meningococci following some other type of bacterial or viral process.

The history of one patient is of interest in that he may have had a prolonged, relatively mild, generalized meningococcus infection for two months before evidence of meningitis appeared.

J. W. (No. 15, Table I). Two months before admission the patient developed some "spots" on his legs and, at the same time, had malaise, fever and sweating. Successive mild exacerbations of this condition occurred for about five weeks. There was also stiffness and soreness of the legs and a tender left ankle. He improved for about two weeks and then, one week before admission, became sick again with headache, stiff neck, and chilly sensations. He was admitted in the condition just described. At no time was his illness severe or critical. He lost 21 pounds in weight in two months.

2. Cases in which the onset was also initiated by symptoms referable to the upper respiratory tract, but which differed from the first group in that the onset was more severe and the time between the first symptoms and meningitis was only a few days.

J. O. (No. 18, Table I). Five days before admission he became acutely ill with malaise and had a temperature of 104°F. There were no localizing signs. The next two days were followed by continued improvement. On the third day, being free from symptoms and without fever, the patient returned to work. In the late afternoon, however, the temperature again rose to 104°F. and prostration was marked. Again no evidence of meningitis was made out by the attending physician. On the morning of the day of admission the patient was mildly delirious, hyperesthesia was marked, and his neck had become stiff.

The present illness in 4 patients was similar to the one just described, and conforms in many respects to the sequence of events described by Herrick (3), consisting of initial involvement of the respiratory tract, an invasive stage, and a stage of metastatic localization in the meninges.

3. In the third group of cases the onset was sudden, and sometimes explosive, with symptoms directly and primarily referable to meningitis. There was no history of any preceding infection in the nose or throat.

L. M. (No. 10, Table I). On the day before admission the patient awoke in the morning with severe headache followed by vomiting. During the day toxicity became marked. On the next day, she became very restless, hyperesthesia appeared, and she was semi-delirious at the time of arrival at the hospital.

J. J. (No. 13, Table I). Eighteen hours before admission to the hospital, the patient developed acute headache, vomiting, and malaise. In the evening of the same day he became stuporous and was brought to the hospital the next morning.

R. C. (No. 9, Table I). Onset four days before admission with severe headache and anorexia. The next day there were periods of delirium and she complained

of being deaf. She was comatose on arrival at the hospital and died fifteen hours after admission.

Ten patients developed meningitis with primary symptoms of headache, stiff neck, vomiting, fever and malaise, usually followed by delirium. The disease appeared suddenly and without prodromal symptoms in otherwise healthy individuals.

This group contributed the more severe type of cases. By contrast, the disease in the first group seemed to be milder; only one patient was markedly delirious and in none were the complications severe. One can only speculate as to the effect which the antecedent local respiratory infection may have had in limiting the infection in the first group, whereas those of the latter group were suddenly subjected to rapid invasion by meningococci.

FINDINGS ON ADMISSION AND CLINICAL COURSE

The presence of some or all of the classical signs, symptoms and laboratory findings, of meningococcus meningitis in the patients established the correct diagnosis usually without difficulty. Numerous authors on the subject have stressed variations in the frequency of the occurrence of the several manifestations of the infection in different outbreaks. The important findings in the present group of patients are recorded in Table I. A description of some of the aspects of the disease follows:

NEUROLOGICAL. Almost all of the patients presented some acute alteration in the sensorium. Fourteen had definite *delirium* ranging from transient episodes of disorientation to more protracted periods of violent purposeless activity. As a rule, the patients who had severe delirium did not remember, after recovery, having been admitted to the hospital. The rapid clearing of delirium was one of the striking features of recovery.

Rigidity of the neck muscles, occasional opisthotonus in the children, and a *positive Kernig's sign* were commonly noted; headache and vomiting were regularly present.

Motor paralysis was strikingly absent. As regards the external ocular muscles, only one patient had involvement, and this consisted of transient external strabismus. The restlessness and de-

NO.	PATIENT HIST. NO. DATE OF ADM. (1935)	SEX (AGE IN YEARS)	COLOR	DAY OF DISEASE ON ADM.*	HEMORR. SKIN	DELIRIUM	JOINTS	EYES	OTHER COMPLICATIONS
? 1	J. B. No. 62168 May 2	M 3	C	1st	+	+	−	Retinal hemorrhage	−
2	G. W. No. 61509 Apr. 1	M 5	C	4th	+	+	−	Ophthalmitis	Serum nesis
3	E. E. No. 61545 Apr. 2	M 5	W	7th	−	+	−	Retinal hemorrhage	−
4	C. S. No. 61207 Mar. 15	F 7	C	2nd	−	−	+	−	−
5	A. S. No. 60439 Feb. 2	M 8	W	3rd	−	+	+	−	Pneum Otiti dia
6	F. G. No. 60845 Feb. 24	F 9	C	6th	−	−	−	Subconjunctival hemorrhage	−
7	O. M. No. 60873 Feb. 25	M 10	W	4th	+	+	+	Conjunctival petechiae	Serum nesis
8	M. F. No. 61972 Apr. 24	F 12	W	3rd	+	+	−	−	Serum nesis
9	R. C. No. 61000 Mar. 4	F 16	C	4th	+	+	−	−	−
10	L. M. No. 61709 Apr. 10	F 17	W	2nd	+	+	−	−	−

* Estimated on the basis of the beginning of definite acute symptoms which may be reasonably
† Estimated on the basis of clear evidence of progressive improvement but before complete
‡ I.V. signifies intravenous route.
§ I.Sp. signifies intraspinous route.

	SPINAL FLUID ON ADMISSION			SERUM THERAPY		APPROX. DURATION OF ACTIVE INFECTION†	COMMENTS
	W.B.C.	Meningococci: Smear	Meningococci: Cult.	I.V.‡	I.Sp.§		
				cc.	*cc.*	*days*	
+	10,250	+	+	40	40	3	Rapid improvement
−	9,000	+	+	120 10 conc.	240 80 conc.	35	Recrudescence. Permanent blindness in right eye
−	2,100	+	+	40	50	9	Rapid improvement
−	18,000	+	+	20 conc.	70 conc.	5	Opisthotonus very marked
+	4,250	+	+	40 30 conc.	50 50 conc.	13	Infection of ear due to pneumonia type III. Deafness bilateral
−	14,680	+	+	40	130	9	Transient spinal block seventh day
+	21,350	+	+	20	240	8	Prolonged mild febrile course Serum sickness?
−	5,650	?	+	40	40 114 conc.	56	Two relapses, approximately 3 weeks apart
+	27,200	+	+	60	60	Died day of admission	No response to therapy
−	29,000	+	−	20 conc.	50 conc.	4–5	Rapid improvement

ed to meningococcus infection.
normal.

TAB

NO.	PATIENT HIST. NO. DATE OF ADM. (1935)	SEX (AGE IN YEARS)	COLOR	DAY OF DISEASE ON ADM.*	SKIN ERUPTION	DELIRIUM	JOINTS	EYES	OTHER CONDITIONS
11	L. S. No. 61868 Apr. 18	F 19	W	1st	+	−	+	Conjunctivitis	Serum sickness
12	R. B. No. 62221 May 4	M 19	C	1st	+	+	+	Ophthalmitis	Epididymitis
13	J. J. No. 61741 Apr. 11	M 22	C	2nd	+	+	+	Perioptic neuritis	Serum sickness
14	N. M. No. 62070 Apr. 28	M 22	C	2nd	+	+	−	−	−
15	J. W. No. 60663 Feb. 14	M 27	W	7th?	−	−	−	−	Epididymitis
16	O. F. No. 62268 May 7	M 27	C	3rd	−	−	−	−	−
17	B. W. No. 61902	M 28	C	2nd	+	+	+	Subconjunctival hemorrhage	−
18	J. O. No. 60763 Feb. 19	M 35	W	5th	−	+	−	Subconjunctival hemorrhage	−
19	L. R. No. 28225 Feb. 28	F 42	W	21st?	−	−	−	−	−
20	W. H. No. 62290 Apr. 8	M 48	C	2nd	−	+	+	−	−
21	M. K. No. 59969 Jan. 7	F 52	W	7th	−	−	+	−	−

TABLE I—concluded

SPINAL FLUID ON ADMISSION			SERUM THERAPY		APPROX. DURATION OF ACTIVE INFECTION†	COMMENTS
W.B.C.	Meningococci: Smear	Meningococci: Cult.	I.V.‡	I.Sp.§		
			cc.	*cc.*	*days*	
5	−	+	50 conc.	−	3	General infection without purulent meningitis
150	+	+	60 conc.	240 conc.	10–12	Permanent blindness in right eye
13,200	+	+	40	220	5	Prolonged arthritis
4,000	+	+	40	120	5	Rapid improvement
2,600	+	+	−	−	10	Mild case. Very sensitive to serum
14,500	+	+	40 conc.	170 conc.	13	Recrudescence
18,000	+	+	20 conc.	120 50 conc.	5	Violent delirium on admission
3,400	−	+	40	60	7	Rapid improvement
156	−	−	−	60	25	Relatively mild case
4,850	+	+	80 conc.	135 conc.	7	Comatose on admission
1,080	−	+	70	60	12	Relatively mild case

lirium, however, often made it impossible to determine with accuracy conditions requiring voluntary coöperation. In one other patient partial left-sided facial weakness was noted for two days as the disease was subsiding.

Hyperesthesia, generalized, was present in most of the patients and manifested itself by painful response to physical examination and nursing care. The *deep reflexes* were usually normal or diminished. Less frequently they were hyperactive. In some instances the activity of the arms differed from that of the legs; or the arm and leg of one side were more active than those of the other. Babinski's sign was uniformly absent.

EYES. There were several types of involvement of the eyes. They consisted of petechial spots in the conjunctivae, subconjunctival hemorrhages, purulent conjunctivitis, hemorrhages into the retina, choked disc, perineuritis with secondary oedema of the disc, and endophthalmitis with vitreous abscess. One or more of these conditions were present in ten of our patients. The minute petechiae and the larger hemorrhages are in consonance with the types of skin eruption. The inflammatory manifestations were undoubtedly due to meningococcus infection. Conjunctivitis subsided rapidly with the other signs of infection and left no permanent change. Two patients (No. 2 and No. 12) developed a unilateral endophthalmitis with vitreous abscess formation. In each instance the right eye was involved. Complete and permanent blindness of the affected side followed the infection. One of these patients, a child of five years, had choked disc and retinal hemorrhage in the other eye, which, however, cleared up completely without affecting the vision. At the time of discharge from the hospital, the seriously affected eye afforded no vision but gave no pain, and evidence of inflammation had completely subsided. The other patient, a colored man of 19 years, continued to have distressing pain in the affected eye even after the active process had completely subsided. Enucleation was done before final discharge.

EARS. Permanent, bilateral complete deafness occurred in one patient (No. 5, Table I). He was suffering from right-sided acute otitis media at the time of admission. Pneumococcus type III was recovered from pus obtained at paracentesis. Since the deafness was bilateral, it probably was due to the meningococcus infection.

SPINAL BLOCK. In two patients (No 2 and No. 6, Table I) during the course of repeated lumbar drainage and treatments, blockage of the flow of spinal fluid occurred. Puncture of the cisterna magna was then performed and the fluid flowed freely, indicating that the block was in the spinal canal. After a few days, in each case, a subsequent lumbar puncture was done and the normal flow of spinal fluid showed that the block had disappeared. In the two patients just mentioned drainage and the administration of serum were carried out through the cisternal route during the period of spinal obstruction.

SKIN ERUPTION. Eleven (52 per cent) had cutaneous petechiae, or small purpuric spots. Two others had a scattered, scanty macular eruption. In no instance did the skin eruption amount to a massive purpura or large cutaneous hemorrhages such as has been described in severe epidemics.

ARTHRITIS. Involvement of the joints was one of the striking features of the cases of 1935. Nine (43 per cent) developed arthritis with pain, swelling, and signs of fluid in the affected joint and two others had pain in several joints without demonstrable changes. The affected joints were characterized by swelling, accumulation of fluid, and variable degrees of tenderness. Redness and increased local heat were not remarkable in any case and were frequently minimal. The affection most commonly involved the knees where it was most severe; the wrists were second choice. In every instance the arthritis, when it occurred, was polyarticular, although the degree differed in the several joints. In one instance, there was a large fluctuant swelling of the soft tissues on the dorsum of the hand which appeared not to be associated with any joint and subsided spontaneously after a week.

The arthritis, in some instances, was present during the acute stage, at the time of admission, while in others it apppeared as the meningitis was beginning to subside. One or more of the joints of six patients were tapped. Each time the character of the fluid was the same; it consisted of thick, very cloudy material, rich in polymorphonuclear leucocytes. Organisms were difficult to find on direct examination and from the joint fluids of only three patients were meningococci successfully cultivated. The time of appearance of the arthritis and the extreme purulent character of the exudate made

it unlikely that the arthritis was a manifestation of serum sickness, even though meningococci were sometimes not proved to be present.

The joints, especially the knees which were more severely involved, were relatively slow in returning to normal, usually requiring ten days to two weeks longer than the meningitis. In one patient discomfort and limitation of motion persisted for several weeks after discharge from the hospital. Recovery was complete, however, in every instance, without permanent residue of disability or x-ray evidence of alteration in the articular surfaces.

Although the arthritis regularly disappeared during convalescence, the best method of hastening recovery was not satisfactorily settled. The affected joints, which were tapped only once or not at all, seem to subside as readily, or even better, than others which were tapped repeatedly as the fluid reaccumulated. When excessive pain, due to distension of the capsule, was present, tapping gave relief, although, sometimes, the alleviation was disappointingly transient.

EPIDIDYMITIS. Two patients (No. 12 and No. 15, Table I) developed swelling in the scrotum due to involvement of the epididymis. In one case, the swelling was unusually large. There was little or no increased heat or redness of the scrotum and the pain was not severe. The condition subsided spontaneously within four or five days.

RECRUDESCENCES AND RELAPSE. Two patients (No. 2 and No. 16, Table I) were considered to have had a recrudescence of the meningitis. The condition was characterized by a reappearance of meningococci in the spinal fluid and an exacerbation of symptoms after temporary improvement for a few days. Recovery had not, however, occurred and in both cases the problem arose of some possible unrecognized local process either in the central nervous system or metastatic elsewhere in the body. The reappearance of meningococci in the spinal fluid served as an indication for return to serum therapy, which was followed by prompt and complete recovery.

One patient (No. 8, Table I) had two definite relapses. She apparently recovered uneventfully from the initial attack which had brought her to the hospital. In the third week of a satisfactory convalescence, after she had had a normal temperature for fifteen days and her spinal fluid had returned to normal, she suddenly developed

fever, headache and malaise, and exhibited the classical signs of meningitis. Her spinal fluid was again cloudy; it contained 10,000 cells per cm. predominantly polymorphonuclear, and meningococci were present in moderate numbers. After desensitization to serum, five intraspinal injections were given, and improvement was definite within forty-eight hours. All evidence of active infection again disappeared and her spinal fluid was normal by the tenth day after the first relapse. In spite of the fact that she seemed well, however, an unexplained tachycardia persisted. There was no evidence of endocarditis. On the twenty-fifth day of normal temperature following the first relapse she was suddenly taken again with fever, headache, and stiffness of the neck. Her spinal fluid was again cloudy, 10,900 cells per cm., and meningococci were present. The readministration of serum intraspinously in four doses was followed by rapid recovery from the second relapse.

All attempts to find a local meningococcic infection in the nasopharynx and sinuses were unsuccessful. Tonsillectomy was eventually performed and the patient was well forty-one days after the second relapse.

HERPES. Herpes Febrilis occurred in approximately half the cases. In some instances the eruption was present at the height of the illness and in others it appeared as the disease was subsiding. In one patient (No. 21, Table I) previously referred to, a confluent eruption, on the lips and inside the mouth, preceded by several days the appearance of meningeal signs.

LABORATORY FINDINGS

BLOOD CULTURES. Blood cultures were taken routinely on each patient at the time of admission. Plain meat infusion broth containing 0.05 per cent dextrose, and meat infusion agar were used. Blood was added in 1 and 2 c.c. amounts to tubes of melted agar, thoroughly mixed, and plates were poured for quantitative estimation as determined by the number of colonies. 10 to 15 c.c. of blood were introduced into flasks containing 100 c.c. of broth.

Seven of the 21 recent cases (33.3 per cent) gave positive blood cultures. One of the five cases of previous years had a positive culture. When meningococci appeared in the blood cultures they

were present only in the flasks of broth. The absence of colonies from the plates indicates that the number of organisms in the blood stream may have been too few to be met with in a random sample of 1 or 2 c.c. of blood. That the agar used for culture was satisfactory was indicated by the fact that the meningococci from the spinal fluid grew well both in poured plates and on the surface.

The percentage of positive blood cultures is approximately the same as the 25 to 30 per cent reported (4) as the average frequency of bacteremia.

SPINAL FLUID. *Meningococci.* Examination of the spinal fluid for meningococci was made routinely by direct examination of stained smears of the centrifuged sediment and also by cultures on the surface of blood agar. In 20 of the 21 recent cases and in each of the 5 cases of former years meningococci were either seen in the stained smear of the sediment or were successfully cultivated. There was a great difference among the cases in the number of organisms in the first sample of spinal fluid. In four instances meningococci could not be seen in smears and in several specimens characteristic bacterial forms were found only after prolonged search. From all but one of the specimens, however, meningococci were cultivated. The spinal fluid from other cases contained large numbers of Gram-negative cocci, each microscopical field showing both extra-cellular and intracellular organisms. It is interesting to note that there appeared to be no consistent correlation between the number of organisms in the first sample of spinal fluid and the severity or course of the disease. Patients whose spinal fluid contained large numbers of meningococci in some instances fared better and in others went through a more prolonged illness than patients in whose fluid organisms were extremely scarce.

In one instance, meningococci were cultured from a spinal fluid which in other respects was normal. The patient (No. 11, Table I) had a lumbar puncture done within fifteen hours after the onset of the acute illness which began with a conjunctivitis rapidly followed by acute general manifestations. The spinal fluid was normal by the usual tests; only 2 cells per cm. were present. Organisms were not demonstrable by direct microscopical examination. Typical meningococci were obtained from the clear spinal fluid by artificial cultiva-

tion. Meningococci were recovered from the blood of this patient and also from conjunctival pus and from purulent fluid drawn from a knee-joint. Rapid recovery followed the administration of antimeningococcus serum intravenously. In this patient, therefore, with a generalized meningococcus infection, even though the bacteria were present in the spinal fluid there was no demonstrable evidence of an inflammatory reaction in the meninges.

Serological grouping of meningococci. Although serological typing of the strains was not carried out in this laboratory, cultures from several of the patients were sent to Dr. M. B. Kirkbride of the New York State Board of Health Laboratories and to Dr. G. W. Rake of the Rockefeller Institute for Medical Research. Both of these investigators have identified the organisms serologically and have very kindly sent reports which uniformly place the strains in the group designated I-III, or I.

CELL COUNT. The average number of white blood cells in the first sample of spinal fluid was approximately 10,000 per cm. The highest initial count was 29,000 per cm. and the lowest 150 per cm. The patient with only 150 cells per cm. was admitted on the first day of the disease. In a second specimen, obtained five hours after the first, the number of cells had risen to 1,120 per cm.

Polymorphonuclear leucocytes predominated and averaged, before serum treatment, approximately 80 to 90 per cent of the total.

In an analysis of the relation between the severity of the illness and the total number of cells present in the first sample of spinal fluid, only a very broad correlation was noted. In general, the degree of inflammatory reaction, as measured by the outpouring of cells, reflected the intensity of the infection. However, exceptions were so frequently encountered that the character of the spinal fluid was not found to be a reliable index of the severity of the disease.

Subsequent reference will be made to the importance of progressive changes in the cell count as a guide to serum treatment.

SERUM THERAPY

Antimeningococcus serum was used in the treatment of all but one of the patients included in this report. Before giving a description of the procedure employed it is a pleasure to acknowledge our indebted-

ness to Dr. A. B. Wadsworth and Dr. Mary B. Kirkbride of the New York State Board of Health, Albany, New York. Dr. Wadsworth and Dr. Kirkbride generously supplied the serum which was used.[1] Their coöperation made it possible to have continuously available a reliable product, the efficacy of which is indicated by the results to be presented. The method of preparation of the polyvalent serum has been described by Wadsworth and Kirkbride (5).

Of the 21 patients of 1935, one died. The New York State serum was also used in the six sporadic cases of the previous four years. Recovery took place in all.

One of the 21 patients of 1935 presented the clinical picture of meningococcus meningitis, but organisms were not demonstrated. Another patient with mild infection was not treated with serum. These two cases are not included in the consideration of the result of serum therapy. The final result is, therefore, one death among nineteen proven cases of acute meningococcus infection in 1935, a mortality of 5.2 per cent, and a 4 per cent mortality in the twenty-five cases of the past five years.

In an analysis of these favorable results certain factors deserve comment. It may be noted from the Table that treatment was begun in nine patients on the first or second day of the disease. The enhanced value of the early administration of any effective therapeutic serum in infection is well established. Consequently, the opportunity to begin to treat almost half of the patients within forty-eight hours after onset undoubtedly influenced the results. It should also be noted that none of the patients had any other debilitating disease to increase the hazards of acute bacterial infection.

Even though the factors, just mentioned, are important in promoting recovery, the efficacy of the serum cannot be minimized. It would be difficult to ascribe the rapid improvement which occurred in some of the patients, who were seriously ill, to any circumstance except the effectiveness of the antimeningococcus serum.

With the patients treated in the spring of 1935, a general policy

[1] One patient (No. 6, Table I) was treated with Type I specific antimeningococcus serum kindly supplied by Dr. G. W. Rake of the Rockefeller Institute for Medical Research.

was adopted which consisted of injections of serum every six hours for the first twenty-four to forty-eight hours. At the first and second treatments, serum was administered both intravenously and intraspinously. The intraspinous treatment, always preceded by complete drainage of the purulent spinal fluid, was then usually continued every six hours for four or more doses. If the cases were extremely severe, or if the blood culture was positive, or if ocular inflammations were present, the intravenous injections were often repeated along with the intraspinous treatments until improvement was definite. After the first twenty-four to forty-eight hours subsequent treatment was determined by the condition of the patient and the character of the spinal fluid. Usually, in cases progressing satisfactorily, spinal drainage followed by serum administration was carried out two or three times on the third and fourth days. Then spinal drainage alone once or twice for the next day or two. Finally, a tap at four or five day intervals to observe the return of the spinal fluid to normal. The procedure just described is similar in some respects to that advocated by Herrick (3).

It should be emphasized that there were many deviations from the procedure just outlined. In some instances improvement was so marked after the first day that the frequency of treatment was promptly decreased. In others, when the severity of the illness remained unchanged for several days, the intensive method was continued without change until improvement became manifest. In the opinion of the authors, it seemed desirable to lengthen the interval between lumbar punctures just as soon as the indications of a subsiding infection were established.

Dr. Wadsworth and Dr. Kirkbride kindly supplied both concentrated and unconcentrated sera. The usual dose of the unconcentrated serum, both intravenously and intraspinously, was 20 c.c. The amount given intraspinously was always 5 c.c. less than the amount of spinal fluid withdrawn. The concentrated preparations were given in 10 c.c. doses. In the Table the total amounts are given, from which, on the basis of dosage, the number of injections may be estimated. The average consisted of 2 to 4 doses intravenously and 8 to 12 doses intraspinously.

Ten of the patients received only unconcentrated serum, six re-

ceived only concentrated material, and four received both. The number of cases of each is too few to afford a comparison between the two types of sera. They both appeared to be equally helpful. The only suggestive difference appeared to be that the concentrated serum may have been slightly irritating to the meninges, since it gave a more marked cellular reaction following intraspinous injection. Five patients suffered from classical serum sickness. Two of these had received unconcentrated serum, one had received concentrated serum, and two had received both types of serum.

As regards the condition of the patient, the factors that were considered helpful in evaluating improvement consisted in clearing of delirium or restlessness, decrease or disappearance of hyperesthesia and headache, and coöperation in taking food and fluids. The course of the temperature was often not a reliable index of favorable progress or the reverse. In some instances, patients who were desperately ill showed very little febrile reaction. In others wide daily swings in the degree of fever undoubtedly were influenced by the serum therapy.

One of the most helpful procedures in estimating the course of the infection consisted in determining changes in the total cell count of the spinal fluid. When the number of cells progressively decreased, it usually indicated that the infection was subsiding. Often after the first injection or two of serum the count sharply increased. This did not persist, however, and when the number of cells was found to be declining by several thousand in samples of fluid obtained on successive punctures, the interval between punctures was prolonged, or even stopped for several days.

In some instances the decrease in the number of bacteria in successive samples of spinal fluid was definite enough to be indicative of a subsiding infection. Since, however, meningococci were, in many cases, difficult to find even in the acute stages of infection, changes in their number often could not be measured. Consequently, the prompt examination of stained smears of the several specimens of spinal fluid for bacteria did not regularly assist in evaluating the course of the infection.

One other aspect of the treatment, which deserves comment, is spinal drainage. In the opinion of the authors, this procedure, of itself, was beneficial. Its value appeared to be particularly definite

when the spinal pressure was markedly increased and headache was severe. In some patients delirium disappeared for several hours following treatment. Two patients begged for spinal puncture in order to obtain relief from unbearable headache.

SUMMARY

This is a report of 26 cases of acute meningococcus meningitis. In all but one of the patients meningococci were isolated either from the blood or from the spinal fluid or from both.

Twenty-one of the patients were admitted to the hospital during the first few months of 1935, at a time when there was an increased incidence of meningitis in the general population. Five of the cases were sporadic during the years 1930 to 1934. There appeared to be no noticeable differences in the presenting signs or symptoms, or in the severity of the disease between the "epidemic" and the sporadic cases. The detailed data, presented in this article, are essentially limited to the findings in the cases observed in 1935.

The illness in ten of the patients began with symptoms referable to the upper respiratory tract. The interval between rhinopharyngitis and evidence of meningitis varied from a few days to two or three weeks. Ten other patients were seized suddenly with meningitis without prodromal symptoms. One patient may have had a relatively mild general meningococcus infection for two months before signs of meningitis appeared.

Among the twenty-one recent patients:

Seven had *bacteremia* (33.3 per cent).

Fourteen had *delirium* (66.6 per cent).

Eleven had a *petechial eruption* (52 per cent).

Two had *reactivation* of meningitis before the first attack had subsided; one had two *relapses*, the infection reappearing each time several weeks after apparently complete recovery from the previous attack (1.3 per cent).

One had complete and permanent bilateral *deafness* (0.4 per cent).

Extrameningeal complications consisted of:

Arthritis in nine patients (43 per cent).

Conjunctivitis in three, and *endophthalmitis* with *vitreous abscess*

in two patients (2.3 per cent). Permanent blindness resulted from the ophthalmitis.

Epididymitis in two patients (0.9 per cent).

Antimeningococcus serum supplied by the Laboratories of the New York State Board of Health, Albany, New York, was regularly employed in therapy.

Early in the treatment, serum was administered both intravenously and intraspinously at six-hour intervals. Later in the course, the route and frequency of injections was determined by the condition of the patient and the laboratory examinations.

Twenty of the twenty-one patients of 1935, and all of the patients of the previous four years, recovered. It is recognized that the number of patients treated is insufficient to justify any undue emphasis on the favorable results. However, the striking recovery of the patients, who were seriously ill, in all probability depended upon the efficacy of the antimeningococcus serum employed.

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